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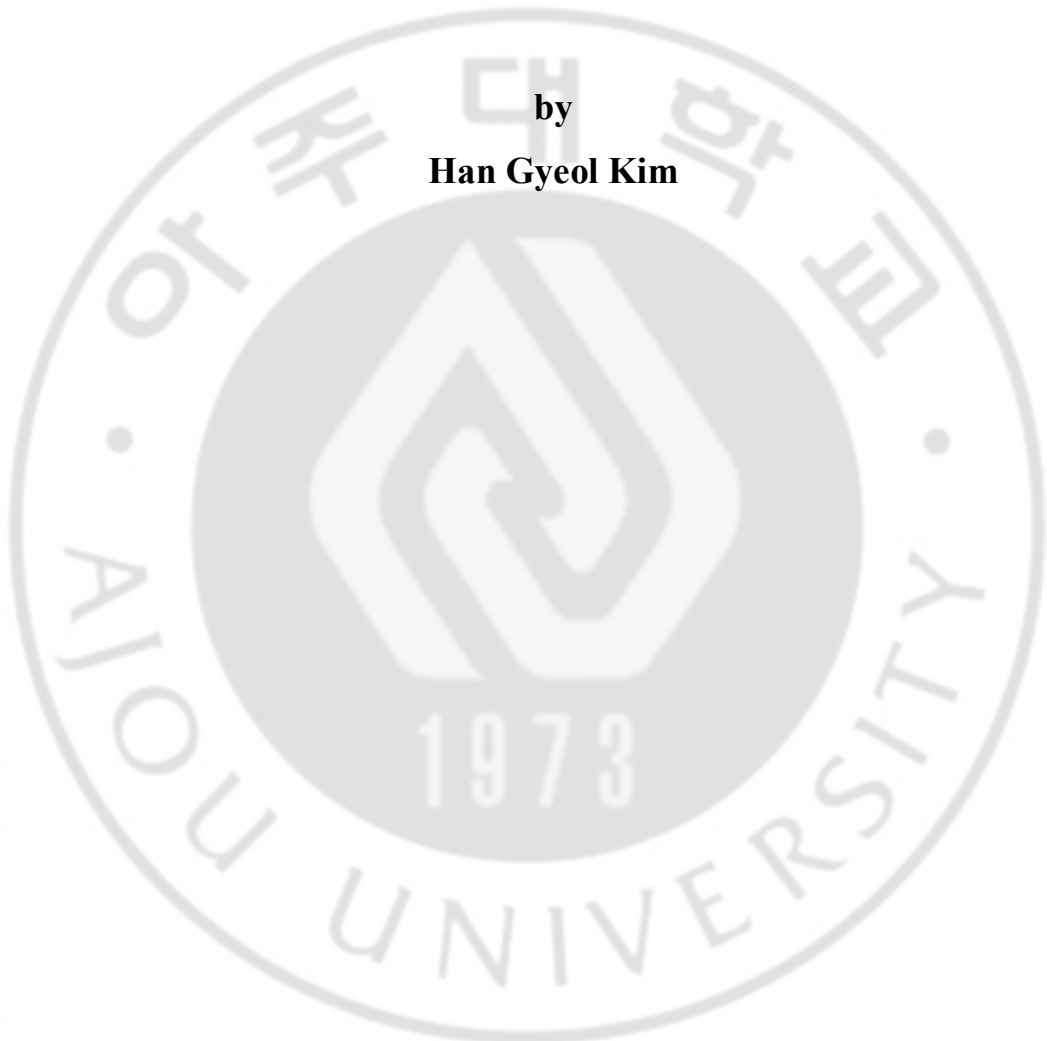
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**G-Protein Beta3 Subunit C825T Polymorphism in Patients
With Overlap Syndrome of Functional Dyspepsia and
Irritable Bowel Syndrome**

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G-Protein Beta3 Subunit C825T Polymorphism in Patients With Overlap Syndrome of Functional Dyspepsia and Irritable Bowel Syndrome.

Background: G-protein beta3 subunit (GNB3) C825T polymorphism alters intracellular signal transduction, which may lead to motor or sensory abnormalities of the gastrointestinal tract. The aim of the present study was to evaluate the association of the GNB3 C825T polymorphism with susceptibility to overlap syndrome of functional dyspepsia (FD) and irritable bowel syndrome (IBS) in a Korean population.

Methods: One hundred sixty-seven patients with FD alone, 60 patients with IBS alone, 85 patients with the overlap of FD and IBS, and 434 asymptomatic healthy subjects participated in the study. Genotyping for GNB3 C825T polymorphism was performed using their blood samples.

Results: No association of genotype in subjects with FD alone, IBS alone or overlap phenotype compared to that in controls was detected. The frequency of GNB3 C825T CT and TT genotypes relative to the CC genotype for the phenotypes of FD alone, IBS alone, and the coexistence of FD and IBS did not significantly differ. Comparison of the TT genotype with the CC/CT genotype showed no significant association for each phenotype group.

Conclusions: There is no apparent association of the GNB3 C825T polymorphism with the susceptibility to FD, IBS or the overlap of FD and IBS. A larger-scale study and further investigation on other candidate genes are required.

Keyword: Functional dyspepsia, Irritable bowel syndrome, G-protein beta3 subunit

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I. INTRODUCTION

Familial aggregation of patients with functional gastrointestinal disorders indicates that susceptibility to functional gastrointestinal disorders may be influenced by hereditary factors (Locke et al., 2000). Genetic variations of potential modulators of gastrointestinal sensory and motor function appear to influence the genesis of symptoms in patients with functional gastrointestinal disorders. There are twin studies that have shown that identical twins will have a greater concordance of having irritable bowel syndrome (IBS) than dizygotic twins, suggesting that genetic factors may contribute to the pathogenesis of IBS (Bengtson et al., 2006). However, the susceptibility genes for functional gastrointestinal disorders are unknown yet and remain to be identified.

Guanine nucleotide binding protein (G protein), beta polypeptide 3 (GNB3) gene is known to be associated with functional dyspepsia (FD) or IBS. A common C825T polymorphism has been described in the gene GNB3 that encodes the beta3 subunit of heterotrimeric G-proteins. This polymorphism gives rise to 3 possible genotypes (C/C, T/C and T/T). The 825T allele of the T/C or T/T genotype is associated with alternative splicing of the gene and the formation of a truncated but functionally active splice variant. Studies on the genetic variation associated with FD and IBS have produced inconsistent results, which is probably attributable to a complex multi-factorial pathophysiology and ethnic differences. For example, the C/C genotype of C825T polymorphism is associated with unexplained dyspepsia in Germany (Holtmann et al., 2004). Whereas, homozygous T or C alleles of the GNB3 C825T polymorphism is associated with meal-unrelated dyspepsia in a U.S. community (Camilleri et al., 2006). Tertiary referral FD in the Netherlands and dyspepsia in the *H. pylori*-negative Japanese population are reported to be associated with the 825T allele of the GNB3 gene (van Lelyveld et al., 2008; Tahara et al., 2008). GNB3 C825T polymorphism is not associated with lower functional gastrointestinal disorders (Andresen et al., 2006).

The 825T allele is believed to be associated with enhanced G-protein activation and, thereby, increased cellular or physiologic responses (Baumgart et al., 1999). Homozygous 825C allele carriers (C/C genotype) are characterized by diminished signal transduction

responses. Evidence shows that the GNB3 status is associated with depression(Zill et al., 2000), increased immune cell activation(Lindemaann et al., 2001), and altered activation of α_2 -adrenoreceptors(Baumgart et al., 1999). A diminished or increased signal transduction response could lead to motor or sensory abnormalities of the gastrointestinal tract that can be pathophysiologic mechanisms underlying FD and IBS(Holtmann et al., 2000). FD and IBS are highly prevalent diseases comprising 10 to 25% of the general population(Locke, 1996). These two conditions commonly coexist(Agreus et al., 1995; Caballero-Plasencia et al., 1999). Clinical studies regarding the pathophysiology of FD and IBS have identified a number of functional abnormalities including disturbances in gastrointestinal motor and sensory function(Coffin et al., 1994; Stanghellini et al., 1996; Tack et al., 1998; Holtmann et al., 1998). The symptom pattern and underlying pathophysiological mechanisms may be different between patients with FD alone compared to patients with both FD and IBS. It has been reported that patients with FD and IBS do not differ in the prevalence of delayed gastric emptying or of impaired gastric accommodation to a meal, but have a greater prevalence of hypersensitivity to gastric distension(Corsetti et al., 2004). Thus, we hypothesized that GNB3 C825T polymorphism, particularly 825T allele, is more likely to be associated with the overlap of FD and IBS rather than FD alone or IBS alone. In the present study, we aimed to study the association of the GNB3 C825T polymorphism with susceptibility to FD alone, IBS alone and the overlap of FD and IBS in a Korean population.

II. MATERIAL AND METHODS

A. Study subjects

Patient cases and control subjects of the study were recruited between January 2007 and December 2008 from visitors to Department of Gastroenterology and the Health Promotion Center of Ajou University Hospital. Subjects without symptoms who visited for health check-up were recruited as healthy controls, and patients with recurrent abdominal symptoms were recruited as patient cases. They underwent examinations including endoscopy, excluded organic causes, and completed a self-administered questionnaire for the diagnosis of FD and IBS according to the ROME III criteria (Tack et al., 2006). All subjects were Koreans. One hundred sixty-seven patients with FD alone, 60 patients with IBS alone, 85 patients with the overlap of FD and IBS, and 434 asymptomatic healthy subjects participated in the study. FD was subclassified into postprandial distress syndrome (PDS), epigastric pain syndrome (EPS), and mixed FD. And IBS was subclassified into IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and mixed IBS (IBS-M). They allowed the use of their blood for the present study. This study was approved by the institutional review board of Ajou University Hospital and written informed consent was obtained from all participants.

B. Questionnaire

The questionnaire included information on demographics and Rome III criteria for the diagnosis of FD and IBS. Dyspeptic symptoms were defined as pain or discomfort in the upper abdomen for the last 3 months, with symptom onset at least 6 months prior to the checkup. IBS was defined as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 2 or more of the following: improvement with defecation, onset associated with a change in stool frequency, or onset associated with a change in stool form.

C. Genotyping

The blood samples were stored at -80°C until use. Genomic DNA was isolated from whole blood using G-DEXTM blood genomic DNA purification kits (Intron Biotechnology Inc., Seongnam, Korea) and quantified using the Picogreen dsDNA quantification reagent according to the standard protocol (Molecular Probes, Eugene, OR, USA). Genotyping was performed using TaqMan Pre-Designed SNP Genotyping Assay (Applied Biosystems, Foster City, CA). The allelic discrimination of SNPs on the basis of the TaqMan technology was performed. Fluorescence is released while the target fragment is amplified by the sequence detection primers. PCR is performed in standard PCR machines and in a real time PCR machine. This platform is particularly well suited for the analysis of a large number of samples with a moderate number of SNPs.

D. Statistical analysis

We presumed that a 10% increase in the prevalence of a genotype would be of clinical relevance. Assuming that a level of significance is 5% ($\alpha=0.05$) and a power is 80% ($\beta=0.80$), a sample of 224 patients and 448 healthy controls would be sufficient to reveal clinically relevant differences. PASS 2005 software (NCSS Kaysville, Utah, USA) was used for the calculation of sample size. Deviations from the Hardy-Weinberg equilibrium (HWE) were checked using chi-square tests. We compared GNB3 genotypes in patients with FD alone, IBS alone and the overlap of FD and IBS vs. asymptomatic controls. And we compared GNB3 genotype with each subgroup vs. asymptomatic controls. The calculation of the odds ratio (OR), 95% confidence intervals (CI) and P values were performed using a multiple logistic regression model after controlling for age and gender as covariates. The p -value threshold for statistical significance used in this study was $P = 0.05$. SAS statistical software (SAS 9.1 and SAS Enterprise Guide 4.1; SAS Institute, Cary, NC, USA) was used for the statistical analysis. A $P < 0.05$ was considered significant.

III. RESULTS

Participant demographics and GNB3 C825T genotype distribution are summarized in Table 1. No significant difference was found between the groups for gender and age. The GNB3 genotype distribution in all study subjects was 196 CC (26.3%), 364 CT (48.8%), and 186 TT (24.9%). This distribution did not deviate from those expected under the Hardy-Weinberg equilibrium ($P > 0.05$). The distribution of allele and genotype frequencies did not differ significantly between males and females.

Table 1. Demographics and genotype distribution in subjects with functional dyspepsia alone, asymptomatic controls, irritable bowel syndrome alone and the overlap of functional dyspepsia and irritable bowel syndrome.

	Group ^a			
	Controls	FD	IBS	Overlap
Gender (M:F [n])	116:267	62:105	25:35	30:55
Mean age (\pm SD), yr	47 (\pm 15)	49 (\pm 15)	43 (\pm 12)	44 (\pm 15)
GNB3 C825T Genotype (n [%])				
CC	112 (25.8)	52 (31.1)	16 (26.7)	16 (18.8)
CT	215 (49.5)	76 (45.4)	31 (51.7)	42 (49.4)
TT	107 (24.7)	39 (23.4)	13 (21.7)	27 (31.8)
Total	434	167	60	85

^aFD: functional dyspepsia alone, Controls: asymptomatic controls, IBS: irritable bowel syndrome alone, Overlap: coexistence of functional dyspepsia and irritable bowel syndrome. GNB3, guanine nucleotide binding protein beta polypeptide 3.

Table 2 shows the results of logistic regression analysis adjusted for age and sex on the association of genotype with each group, compared with asymptomatic controls. No

association of genotype in subjects with FD alone, IBS alone or overlap phenotype compared to that in controls was detected ($P > 0.05$). The odds ratios for the co-dominant, dominant and recessive models are shown in Table 2. The frequency of GNB3 C825T CT and TT genotypes relative to the CC genotype for the phenotypes of FD alone, IBS alone, and the coexistence of FD and IBS did not significantly differ. Comparison of the TT genotype with the CC/CT genotype showed no significant association for each phenotype group.

Table 2. Logistic regression analysis adjusted for age and sex in subjects with functional dyspepsia alone, asymptomatic controls, irritable bowel syndrome alone and the overlap of functional dyspepsia and irritable bowel syndrome.

Model	FD ^a vs Controls ^b		IBS ^c vs Controls		Overlap ^d vs Controls	
	<i>P</i> -value	OR	<i>P</i> -value	OR	<i>P</i> -value	OR
Co-dominant	0.329	1.13	0.723	0.93	0.112	1.31
Dominant	0.718	1.04	0.671	0.93	0.160	1.21
Recessive	0.220	1.13	0.874	0.97	0.234	1.19
MAF	0.321	1.07	0.723	0.97	0.112	1.14

^aFD: functional dyspepsia alone, ^bControls: asymptomatic controls, ^cIBS: irritable bowel syndrome alone, ^dOverlap: coexistence of functional dyspepsia and irritable bowel syndrome. Co-dominant, CC vs CT vs TT; Dominant, CC vs CT and TT; Recessive, CC and CT vs TT; MAF; minor allele frequency.

OR: odd ratio(95% CI)

FD was subclassified into PDS, EPS, and mixed FD. Table 3 shows the results of logistic regression analysis adjusted for age and sex on the association of genotype with each subgroup, compared with asymptomatic controls. No association of genotype in subjects with PDS, EPS, and mixed FD compared to that in controls was detected ($P > 0.05$).

IBS was subclassified into IBS-D, IBS-C, and IBS-M. Table 4 shows the results of logistic regression analysis adjusted for age and sex on the association of genotype with each subgroup, compared with asymptomatic controls. No association of genotype in subjects

with IBS-D, IBS-C, and IBS-M compared to that in controls was detected ($P > 0.05$).

Table 3. Logistic regression analysis adjusted for age and sex in subjects with postprandial distress syndrome, the absence of chronic recurrent abdominal symptoms, epigastric pain syndrome, and the coexistence of postprandial distress syndrome and epigastric pain syndrome.

Model	PDS ^a vs Controls ^b		EPS ^c vs Controls		Mixed ^d vs Controls	
	<i>P</i> -value	OR	<i>P</i> -value	OR	<i>P</i> -value	OR
Co-dominant	0.725	1.09	0.476	0.89	0.634	1.13
Dominant	0.746	1.07	0.533	1.00	0.469	1.13
Recessive	0.801	1.05	0.081	0.80	0.958	1.04
MAF	0.724	1.04	0.471	0.94	0.356	1.06

^aPDS: Postprandial distress syndrome(n=32), ^bControls: asymptomatic controls, ^cEPS: Epigastric pain syndrome(n=93), ^dMixed: coexistence of postprandial distress syndrome and epigastric pain syndrome(n=134).

Co-dominant, CC vs CT vs TT; Dominant, CC vs CT and TT; Recessive, CC and CT vs TT; MAF; minor allele frequency.

OR: odd ratio(95% CI)

Table 4. Logistic regression analysis adjusted for age and sex in subjects with irritable bowel syndrome with diarrhea, the absence of chronic recurrent abdominal symptoms, and irritable bowel syndrome with constipation, and mixed irritable bowel syndrome.

Model	IBS-D ^a vs Controls ^b		IBS-C ^c vs Controls		IBS-M ^d vs Controls	
	<i>P</i> -value	OR	<i>P</i> -value	OR	<i>P</i> -value	OR
Co-dominant	0.553	1.03	0.181	1.30	0.282	1.28
Dominant	0.195	1.31	0.274	1.18	0.105	1.32
Recessive	0.761	0.94	0.274	1.21	0.881	1.02
MAF	0.550	1.06	0.177	1.14	0.274	1.13

^aIBS-D: irritable bowel syndrome with diarrhea(n=44), ^bControls: asymptomatic controls, ^cIBS-C: irritable bowel syndrome with constipation(n=55), ^dIBS-M: mixed irritable bowel syndrome(n=39).

Co-dominant, CC vs CT vs TT; Dominant, CC vs CT and TT; Recessive, CC and CT vs TT; MAF; minor allele frequency.

OR: odd ratio(95% CI)



IV. DISCUSSION

This study evaluated GNB3 C825T polymorphism in a Korean population comprising people with FD alone, IBS alone, the coexistence of FD and IBS, and healthy controls who visited outpatient clinic for abdominal symptoms or a health care unit for annual health check-up. We failed to demonstrate an association between GNB3 C825T polymorphism and the overlap of FD and IBS. Furthermore, no significant association between GNB3 C825T polymorphism and the existence of FD alone or IBS alone was found in the present study. Our findings are consistent with a previous study from a Korean population (Park et al., 2009). In contrast, data from Japan show that homozygous GNB3 825T is associated with Japanese dyspeptic subjects without *H. pylori* infection or with epigastric pain syndrome-like symptomatology (Tahara et al., 2008; Oshima et al., 2010). We explored whether any subgroup of FD or IBS is different from controls since the subgroups of these syndromes are likely to have different pathogenesis and may confound the results. However, we did not find any association of homozygous GNB3 825T with epigastric pain syndrome-like dyspepsia, postprandial distress syndrome-like dyspepsia, IBS-D, or IBS-C.

Similarly, in the West, conflicting results have been reported. While a study from the Netherlands demonstrated that T allele carriers of GNB3 C825T polymorphism are associated with dyspepsia (van Lelyveld et al., 2008), a report in a German population shows that homozygous GNB3 825C status is associated with unexplained dyspepsia (Holtmann et al., 2004). Furthermore, reports from the US revealed that meal-unrelated dyspepsia is associated with both the homozygous GNB3 825T and C genotypes (Camilleri et al., 2006). These contrasting observations may be partially explained by a racial difference and heterogeneity of the disease. In addition, the diagnostic criteria of FD, sample selection or sample size may affect the outcome. T alleles of the GNB3 C825T polymorphism are reported to be more strongly correlated with IBS with constipation in the Korean population (Lee et al., 2010). The study population included 88 control cases and 12 IBS-C cases. This sample size does not appear to be adequate for the study on the association of GNB3 C825T polymorphism with disease susceptibility. Moreover, there is a contradictory

study showing that GNB3 C825T polymorphism is not associated with FD and IBS in Koreans(Park et al., 2009). The study population consisted of 70 healthy controls, 62 FD patients and 49 IBS patients. The number of this study population appears to be too small to show the association of genetic polymorphisms with disease susceptibility. Relatively small sample sizes may produce the type II error. The sample size of the present study is greater than that of the previous Korean studies. Based on the results of the sample size calculation that 224 patients and 448 healthy controls were required, we recruited 312 patients and 434 healthy controls in the present study. However, the number of each group, particularly the number of each subgroup, might be not sufficient.

Disturbed gut sensory or motor function, dysfunction of the autonomic nervous system, and underlying psychiatric disturbance have been suggested to contribute to the pathophysiology of functional gastrointestinal disorders like FD and IBS(Coffin et al., 1994; Stanghellini et al., 1996; Tack et al., 1998; Holtmann et al., 1998; Corsetti et al., 2004). All of these abnormalities may be associated with the alteration of intracellular signal transduction. Approximately up to 80% of all known membrane receptors that are linked to intracellular effector systems are coupled to G proteins(Baumgart et al., 1999; Lindemaann et al., 2001). G proteins play a crucial role in intracellular signal transduction. Therefore, qualitative or quantitative changes in G proteins may lead to functional changes by inhibiting or enhancing intracellular signal transduction. The GNB3 gene encodes the $\beta 3$ subunit of heterotrimeric G-proteins, which is known to potentially affect intracellular signal transduction and biological activity, and the 825T is associated with enhanced G-protein activation(Siffert et al., 1998). Given that patients with FD and IBS do not differ in the prevalence of delayed gastric emptying or of impaired gastric accommodation to a meal, but have a greater prevalence of hypersensitivity to gastric distension(Corsetti et al., 2004), GNB3 C825T polymorphism, particularly 825T allele, is more likely to be associated with the overlap of FD and IBS rather than FD alone or IBS alone. It is conceivable that the GNB3 genotype is involved in the generation of common pathophysiologic mechanisms underlying FD and IBS. Transition of functional gastrointestinal disorders in their natural history supports our hypothesis. To my knowledge, this is the first study investigating the genetic factors of overlap syndrome. However, in the present study, we failed to find the association of the GNB3 polymorphism with the overlap of FD and IBS. Genetic

polymorphisms of other candidate genes warrant further investigation.

The data in the present study are from outpatient clinic of the university hospital and from subjects undergoing health check-up. We selected subjects who underwent upper or lower gastrointestinal endoscopy in order to exclude organic causes. Therefore, uninvestigated subjects were not included in the study. All subjects are Korean. Korean population is known to be genetically homogenous. Although GNB3 C825T polymorphism doesn't have any statistically significant association with FD and IBS in the present study, this negative association might be affected by multiple pathophysiologic mechanisms underlying functional gastrointestinal disorders.



V. CONCLUSION

In conclusion, our findings suggest that there is no apparent association of the GNB3 C825T polymorphism with the susceptibility to FD, IBS or the overlap of FD and IBS. A larger-scale study and further investigation on other candidate genes are required.



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기능성 소화 불량증 및 과민성 장 증후군의 중복 증후군 환자에서 G-Protein Beta3 C825T 유전자 다형성

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김 한 결

(지도교수: 이 광 재)

목적: GNB3 C825T 유전자 다형성은 세포 내 신호전달을 변화시켜 위장관의 운동이나 감각이상을 일으킬 수 있다고 알려져 있다. 본 연구는 한국인을 대상으로 GNB3 C825T 유전자 다형성이 기능성 소화 불량증 및 과민성 장 증후군의 중복 증후군과 어떠한 연관성이 있는지 살펴보고자 시행되었다.

방법: 기능성 소화 불량증 단독군이 169명, 과민성 장 증후군 단독군이 60명이었으며, 중복 증후군 환자는 85명이었다. 이 연구에 참여한 무증상 건강군은 434명이었다.

결과: 각 환자군의 유전자형을 무증상 건강군과 비교하였을 때 서로 유의한 차이가 없는 것으로 나타났으며, 각 환자군에서 GNB3 C825T의 CT와 TT 유전자형의 빈도도 유의한 차이가 없는 것으로 나타났다. 또한 TT 유전자형을 CC/CT 유전자형과 비교하였을 때에도 각 군 간에 유의한 차이를 보이지 않았다.

결론: GNB3 C825T 유전자 다형성은 기능성 소화 불량증과 과민성 장 증후군, 그리고 중복 증후군의 감수성에 있어서 명백한 연관 관계를 보이지 않았다. 추후 대규모의 연구와 다른 유전자와 에 대한 연구가 더 필요할 것이다.

핵심어: 기능성 소화 불량증, 과민성 장 증후군, G-protein beta3 유전자