ORIGINAL PAPER

DOI: https://doi.org/10.20883/jms.2017.248

Clinical features of gastroesophageal reflux disease in children with different genotypes of C825T polymorphic loci of GNB3 gene

Marta Dats-Opoka[1], Halyna Makukh[2]

[1] Department of Propedeutics of Pediatrics and Medical Genetics, Danylo Halytsky Lviv National Medical University, Ukraine
[2] State Institution "Institute of Hereditary Pathology Ukrainian National Academy of Medical Sciences", Ukraine

ABSTRACT

Introduction. Considering the steady growth of the gastroesophageal reflux disease (GERD) in children in recent decades, the difficulty of GERD diagnosing in children, the variety of GERD clinical and morphological features as well as the factors that cause it, including genetic predisposition, a detailed analysis of each of them remains relevant.
Aim. To analyze the peculiarities of nutritional status in children with GERD and its correlation with the different genotypes of C825T polymorphic loci of *GNB3* gene as well as its association with different GERD clinical manifestations.
Material and Methods. The analysis of GERD clinical features was carried out and the nutritional status in 100 children of school age was estimated. Molecular and genetic research of C825T loci of *GNB3* gene using PCR method (rs5443) was carried out in the studied group (100 children) and in 40 healthy children that formed the control group.
Results. The distribution of the genotypes of C825T polymorphic loci of the *GNB3* gene in children with GERD and healthy children in the control group did not have any statistically significant difference ($\chi 2 = 0.27$, $p = 0.87$). Among more than a half of the children in both groups, the *GNB3* 825ST heterozygous genotype were detected (54.0% of the experimental group and 57.5% of the control group), according to de Vries et al. data is a factor of GERD increased risk. The association between the genotype of C825T locus of *GNB3* gene and the data of intragastric endoscopy with pH monitoring was found: in patients with hyperacidic GERD the genotype 825CT was predominantly revealed, and in children with normal and hypoacidic GERD a higher frequency of the 825TT genotype was found. In children with GERD having a lack of the nutritional status (61%), the genotype 825CT (61.82%, $p = 0.013$) and 825TT (100%, $p = 0.005$) of the *GNB3* gene were detected significantly more often.
Conclusions. The distribution of the genotypes of C825T polymorphic loci of the *GNB3* gene in children with GERD was determined. Differences in GERD development depending on the different *GNB3* genotypes were not detected. The distribution of the genotypes of C825T loci of the *GNB3* gene remained unchanged at different GERD clinical manifestations. The presence of 825CT and 825TT genotypes of *GNB3* gene in patients with GERD is associated with a decrease in physical development signs. The association between genotype of C825T loci of *GNB3* gene and pH intragastric endoscopy data was identified: in patients with hyperacidity GERD 825CC genotype was usually found, and in children with normal- and hypoacidity GERD 825TT genotype was usually found.

Keywords: gastroesophageal reflux disease, children, physical development, polymorphism C825T, *GNB3*.

Introduction

Nowadays, it is well-known that gastroesophageal reflux disease (GERD) has a multifactor etiology [1–4]. Patients with GERD may have a normal esophageal acid exposure, but their esophagus mucous membrane may be more sensitive to acid reflux, which leads

to heartburn and erosive esophagitis by visceral and neural dysfunction [5, 6].

Studies showing a higher predisposition to this disease in monozygotic twins, in contrast to the dizygotic twin pairs, point to the leading role of genetically determined factors in the pathogenesis of this disease [7, 8]. Recent studies show that the course of inflammatory reactions of the organism, drug metabolism, DNA reparative processes, mutagenesis, cell cycle regulation processes, and alternative splicing are associated with the risk of GERD and its complications – Barrett's esophagus and adenocarcinoma of the esophagus [9]. The majority of works point to the necessity of the additional research using more samples to make conclusions about the role of certain genes or mechanisms [10].

Heterotrimeric guanine nucleotide binding proteins (G proteins) transmit signals between receptors and effector proteins. Many surface-cell receptors of the neurotransmitters use G-proteins for the transduction of intracellular signaling pathways [11]. The subunits of these proteins are encoded by the entire genetic G family. Beta subunits (encoded by the *GNB3* gene) are important regulators of alpha subunits as well as some signal transductor receptors and effector. Polymorphism in the 10 exons of the *GNB3* 825C/T gene is rather interesting [12]. The single-nucleotide polymorphism of the *GNB3* gene is due to the replacement of cytosine (allele 825C) with thymine (allele 825T). In the presence of the 825T allele there is an alternative splicing: the shorter version of the mRNA called Gb3s is being expressed [13]. In this case, 123 nucleotides are absent in the given mRNA, and as a result, the protein with the deletion of 41 amino acids must be synthesized. Using RT-PCR experiments, the expression of this alternative splicing type of mRNA was confirmed in B-lymphoblasts [12], neutrophils [14], and T-lymphocytes [15].

Recent studies show that the genetic polymorphism of the *GNB3* C825T gene became a factor involved in the chain of mechanisms that cause reflux [16]. The Gb3s type, which is synthesized in the presence of the 825T allele, as reported is associated with depression [17], hypertension [12], obesity [18], medically induced weight gain [19, 20], although some contradictions remain.

Aim

The aim of the research was to study the peculiarities of distribution of the genotypes of C825T polymorphic loci of *GNB3* gene in children with GERD at its different clinical manifestations and depending on the nutritional status markers.

Material and methods

100 children of school age formed the experimental group (mean age 10.8 ± 3.07 years), being cured of GERD in Lviv Regional Children's Clinical Hospital (MI LRCCH "OHMATDYT"). The children included 56 girls (56% ± 9.6%) and 44 boys (44% ± 9.6%).

The protocol of the study was approved by the Ethics committee of the Danylo Halytsky Lviv National Medical University (№ 10 dated December 15, 2014). All patients were informed about the study and provided written informed consent to participate in the research. All children were generally examined, all children had a somatometry with body mass index (BMI) and a standardized index (Z-score), endoscopic examination of the esophagus, stomach and duodenum, using Fujinon WG 88 FP video gastroscope, 21 children had intragastric endoscopy with pH monitoring using acid gastrographer (AG TU U 33.1-13300318-002: 2007, the manufacturer of Start Ltd., Vinnitsa) as well as genetic analysis.

The criteria for inclusion in the research group are as follows:

1) complaints: pain syndrome (rebound pain that is not associated with damage of other organs and systems, and epigastric pain), dyspeptic syndrome (heartburn, nausea, vomiting, eructation), irritable bowel syndrome (constipation, flatulence);
2) the presence of GERD was confirmed endoscopically, according to the Savari-Miller classification in Tytgat GNJ et al., 1990 modification;
3) voluntary informed consent of the parents for the genetic analysis.

Exclusion criteria: refusal to participate in any stage of the study.

As a control, a group of 40 healthy children of the given age (19 boys and 21 girls) was formed. The experimental materials were 40 DNA samples isolated from buccal epithelial cells.

Molecular and genetic study of the polymorphic loci C825T of *GNB3* gene (the number of polymorphism in NCBI database is rs5443) was performed. The gene fragment of the 268 b.p. size was amplified using primers GP-1 (sense, 5-TGACCCACTTGCCACCCGTGC-3') and GP-2 (antisense, 5'-GCAGCAGCCAGGGCTGGC-3'). In result of the PCR product proceeding by endonuclease of BseD1 restriction, fragments sized 268 b.p. – genotype 825TT, 268 b.p., 152 b.p. and 116 b.p. – gen-

otype 825CT, 152 b.p. and 116 b.p. – genotype 825CC, respectively, are visualized on the electrophoregram.

Results and discussion

In result of the study of molecular and genetic analysis of DNA in 100 people of the given group with GERD and 40 people of the control group genotype of the polymorphic loci C825T of *GNB3* gene was determined. More than a half of the children in both groups, the *GNB3* 825CT heterozygous genotype were detected, which according to de Vries et al. data is a factor of GERD increased risk. The results of the carried out molecular and genetic study and statistical analysis are shown in **Table 1.**

Distribution of genotypes of the polymorphic loci C825T of GNB3 gene in children with GERD was similar to the determined in the control group ($\chi 2 = 0,27$, $p = 0,87$). The calculated GERD odds ratios depending on genotype of loci C825T of *GNB3* gene are shown in **Table 1**; all of them are within the insignificant limits. Frequencies indicators of alleles of loci C825T of *GNB3* gene in the studied groups of the children are presented in **Table 2.**

As it is shown in **Table 2,** frequencies of the normal C (69%) and highly functional T (31%) alleles of loci C825T of *GNB3* gene were practically identical both in the studied and in the control groups. It should be mentioned that the determined distribution coincided with the data of other studies in the Caucasian population. Frequency of T allele *GNB3* 825C/T of polymorphism is higher in Asian populations (42–53%), than in Caucasian population (27–42%) [19, 21]. It is known that *GNB3* 825TT is associated with functional dyspepsia in the Japanese [22], in contrast to the western studies. In the Caucasian population genotype of *GNB3* 825CC is associated with functional dyspepsia [23]. In de Vries et al. studies it is shown that GERD is connected to CT genotype genotype of *GNB3* C825T polymorphism compared with CC genotype [16]. Genetic studies of the association for functional dyspepsia have shown results similar to irritable bowel syndrome (IBS), namely: *GNB3* 825T allele can be connected with IBS and constipation in the Koreans [24]. The obtained results coincide with Tadayuki Oshima et al. data: there was no connection between *GNB3* C825T genotype and GERD symptoms [25]. These results point to a significant variations in the genetic effect of *GNB3*, depending on ethnicity.

Besides, we analyzed the frequency of genotypes of loci C825T of *GNB3* gene in children with different GERD stages (**Table 3**).

Table 1. Distribution of genotypes of the polymorphic loci C825T of *GNB3* gene in the studied groups

GNB3 genotype	Studied group, %	Control group, %	χ2	p	OR	
	n = 100	n = 40			Value	95% CI
GNB3 825CC	42.0	40.0	0.27	0.87	1.09	0.51–2.29
GNB3 825CT	54.0	57.5			0.87	0.41–1.82
GNB3 825TT	4.0	2.5			1.63	0.18–15.00

Note: n – number of subjects, P – the significance of the differences in distribution of genotypes between the control and the studied groups, OR – odds ratio

Table 2. Frequency of the alleles of polymorphic loci C825T of *GNB3* gene in the studied groups

GNB3 gene alleles	Frequency, %		χ2	p	OR	
	Studied group, n = 100	Control group, n = 40			value	95% CI
GNB3 825C	69.0	68.8	0.00	0.97	1.01	0.58–1.77
GNB3 825T	31.0	31.3			0.99	0.56–1.73

Note: n – number of subjects, P – the significance of the differences between the control and the studied groups, OR – odds ratio

Table 3. Distribution of genotypes of polymorphic loci C825T of *GNB3* gene depending on the patients' gender

Genotype *GNB3*	Girls		Boys	
	Control group, % (*n = 21*)	Studied group, % (*n = 56*)	Control group, % (*n = 19*)	Studied group, % (*n = 44*)
GNB3 825CC	47.6	35.7	31.6	47.7
GNB3 825CT	47.6	60.7	68.4	47.7
GNB3 825TT	4.8	3.6	0.00	4.5
$\chi 2 = 1.07$, P = 0.59			$\chi 2 = 2.72$, P = 0.26	

Note: n – number of subjects, P – the significance of the differences in genotypes distribution, between the control and the studied groups: * – statistically significant value.

Results of the statistical calculations point to the absence of significant differences in polymorphic loci C825T genotype distribution both between boys and girls of the studied and the control groups, and between the groups ($p > 0.05$).

The distribution of genotypes of the C825T loci of *GNB3* gene in the groups of patients with different GERD clinical manifestations was analyzed. The distribution of genotypes in the groups of patients with esophagitis (I–II stage according Tytgat et al. 1990), without esophagitis, in patients with dyspeptic symptoms and in the presence of an irritable bowel syndrome with constipation (Roman criteria IV) did not differ both from the control group data and among itself (**Table 4**). At comparing the patients with GERD by pH-monitoring results, significant differences in the distribution of C825T loci genotypes of *GNB3* gene ($p < 0.05$) were found. Among the patients with hyperacidic GERD (pH 0.86–1.59), one third had a CC genotype and there was no patients found with a TT genotype, at the same time in a group of the children with normal and hypoacidic GERD (pH 1.60–3.59) 25% of patients had a *GNB3 825*TT genotype. The obtained data indicate the association of the loci C825T genotype of *GNB3* gene with the pH-monitoring data. The probable mechanism of such action requires additional discussion.

In accordance with a number of publications, the presence of T allele is a predisposition to obesity and hypertension factor [26, 27]. It has been shown that in the presence of T allele of C825T loci of *GNB3* gene, there is an alternative splicing and increased expression of m-RNA [28]. However, Ruiz-Velasco V and Ikeda SR in their studies have shown that Gb3s protein, which is expressed from the truncated version, is functionally inactive [29].

According to Tadayuki Oshima et al., the frequency of TT genotype was significantly higher in patients with epigastric pain syndrome. The 825TT genotype, which causes increased transduction of the signal through Gb3s, can be involved in gastroduodenal motility change and dyspeptic symptoms development [25].

Considering a significant number of publications devoted to the association of C825T polymorphism with obesity and insulin resistance, the next aim of the study was to analyze the physical development markers in children with GERD. Determination of BMI (body mass index) and z-score, which displays a deviation from the mean values (**Table 5**) was carried out.

Standardized deviation index (z-score) can be positive or negative. As the data from the **Table 5** show, in all genotype groups z-score mean value is negative that points to a lower than the corresponding normal markers of the nutritional status in children with GERD. BMI and z-score indexes in the groups of GERD patients with different genotype by C825T loci of *GNB3* gene were similar ($p > 0.05$). The difference of BMI mean value between the groups with 825TT and 825CC genotypes approached a meaningful value ($p = 0.08$).

Considering that the spread of the standardized z-score deviation in children with GERD ranged from -4.36 to 1.94, it became important to analyze the proportion of patients with negative (less than average norm) and positive (normal or higher than average

Table 4. Distribution of genotypes of the C825T locus of the *GNB3* gene in the groups of patients with different clinical manifestations of GERD

Group	N (men)	Age mean (s.d.)	BMI mean (s.d.)	Allele distribution			HWE
				CC, N(%)	CT, N (%)	TT, N (%)	
Healthy controls	40 (19)	9.3 ± 3.86	16.12 ± 2.04	16 (40.0%)	24 (57.5%)	1 (2.5%)	no
All GERD patients	100 (44)	10.8 ± 3.07	17.11 ± 2.96	41 (41.0%)	55 (55.0%)	4 (4.0%)	no
hyperacidic GERD	13 (10)	11.7 ± 3.04	16.86 ± 2.07	4 (30.8%)	9(69.2%)	0*	yes
normal and hypoacidic GERD	8 (3)	11.3 ± 3.24	17.25 ± 3.44	0	6(75.0%)	2 (25.0%)*	yes
with esophagitis	64 (34)	11.04 ± 3.03	17.67 ± 3.03	24 (37.5%)	37(57.8%)	3 (4.7%)	yes
without esophagitis	36 (10)	10.31 ± 3.08	16.11 ± 2.55	17 (47.2%)	18 (50.0%)	1 (2.8%)	no
Only GERD symptoms	8 (5)	12.36 ± 2.87	18.69 ± 3.10	1 (12.5%)	7 (87.5%)	0	no
Concomitant FD symptoms	48 (21)	10.76 ± 3.06	17.36 ± 2.60	23 (47.9%)	23 (47.9%)	2 (4.2%)	yes
Concomitant IBS symptoms	17 (6)	10.55 ± 3.21	18.33 ± 3.46	6 (35.3%)	10 (58.8%)	1 (5.9%)	yes
EPS	77 (34)	11.16 ± 3.00	17.41 ± 3.05	34 (44.2%)	40 (51.9%)	3 (3.9%)	no

Note: N – numbe r of subjects; BMI – body mass index; HWE – Hardy-Weinberg equilibrium; yes/no – Hardy-Weinberg $\chi 2 < 3.84$; * – statistically significant value.

Hyperacidic GERD – intragastric pH 0,86–1,59; normal and hypoacidic GERD – intragastric pH 1,60–3,59 (n = 21). Only GERD symptoms: patients with GERD without symptoms of FD or/and IBS. Concomitant FD/IBS symptoms: GERD patients with concomitant symptoms of FD or IBS, respectively. EPS – Epigastric pain syndrome. When added, these groups contain more than the total 100 patients; thisis due to the overlap between FD and IBS: 40 patients had both symptoms of FD and IBS.

Table 5. Nutritional status indexes in children with GERD

Genotype group	BMI			z-score		
	M ± m	min	max	M ± m	min	max
825 CC n = 41	17.11 ± 2.99	12.6	23.0	-0.49 ± 1.28	- 3.41	1.60
825 CT n = 55	17.20 ± 3.06	11.5	24.5	-0.55 ± 1.37	- 4.36	1.94
825 TT n = 4	15.78 ± 1.35	14.7	17.6	-0.48 ± 0.30	- 0.92	-0.28
Total (n = 100)	17.11 ± 2.96	11.5	24.5	-0.52 ± 1.29	-4.36	1.94

n – number; BMI – body mass index; M ± m – mean value and its deviation; min – the minimum value; max – the maximum value; z-score – standardized deviation

Table 6. Z-score in patients with GERD and different genotypes of C825T loci of *GNB3* gene

Genotype group	z-score value				χ2	p
	≥ 0		< 0			
	n	%	n	%		
825 CC (n = 41)	19	46.34	22	53.66	0.44	0.508
825 TC (n = 55)	21	38.18	34	61.82	6.15	0.013*
825 TT (n = 4)	0	0	4	100	8.00	0.005*

n – number; z-score – standard deviation z; * – statistically significant value

norm) values of z-score in patients with different genotypes of *GNB3* gene (**Table 6**).

In the groups of GERD patients with 825TC and 825TT genotypes, the children having lag in physical development were predominant, 62% and 100% of them, respectively. A statistically significant difference concerning the ratio of the patients with negative and positive z-score values in patients with genotypes 825CT and 825TT of *GNB3* gene was found (**Table 6**). Thus, in patients with GERD, the presence of 825CT and 825TT genotype of *GNB3* gene can be considered as a factor of propensity to lowered physical development rates. The obtained results correlate with the found associations concerning pH-monitoring results in patients with GERD.

Conclusions

1) Distribution of the genotypes and the alleles frequency of polymorphic C825T loci of *GNB3* gene in children with GERD, similar to the determined in the control group. The frequency of the allele 825T of *GNB3* gene coincided in the studied group of children with GERD and the control group, and it was 31%.
2) Association between genotype of C825T loci of *GNB3* gene and pH-monitoring data was found: genotype 825CC was determined mostly in the patients with hyperacidic GERD, and in the children with normal and hypoacidic GERD 825TT genotype was found more frequently.
3) Distribution of C825T loci of *GNB3* gene in the groups of patients with esophagitis, without esophagitis, in patients with dyspepsia, and in case of irritable bowel syndrome with constipation did not differ from both the control group data and between itself.
4) In 39% of the patients with GERD a normal value of the nutritional status was determined, while 61% of them characterized by its delay. The presence of 825CT and 825TT genotype of *GNB3* gene in patients with GERD can be considered as a propensity factor to lowered physical development rates.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Holtmann G, Adam B, Liebregts T. Review article: the patient with gastro-oesophageal reflux disease—lifestyle advice and medication. Aliment Pharmacol Ther. 2004;20(Suppl 8):24–7.
2. Terry P, Lagergren J, Wolk A, Nyren O. Reflux-inducing dietary factors and risk of adenocarcinoma of the esophagus and gastric cardia. Nutr Cancer. 2000;38:186–91.
3. Chourasia D, Ghoshal UC. Pathogenesis of gastro-oesophageal reflux disease: what role do Helicobacter pylori and host genetic factors play? Trop Gastroenterol. 2008;29:13–9.

4. Ghoshal UC, Chourasia D. Gastroesophageal reflux disease and Helicobacter pylori: what may be the relationship? J Neurogastroenterol Motil. 2010;16:243–50.
5. Rohof WO, Hirsch DP, Boeckxstaens GE. Pathophysiology and management of gastroesophageal reflux disease. Minerva Gastroenterol Dietol. 2009;55:289–300.
6. Boeckxstaens GE. Review article: the pathophysiology of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;26:149–60.
7. Cameron AJ, Lagergren J, Henriksson C, Nyren O, Locke GR 3rd, Pedersen NL. Gastroesophageal reflux disease in monozygotic and dizygotic twins. Gastroenterology. 2002;122:55–9.
8. Mohammed I, Cherkas LF, Riley SA, Spector TD, Trudgill NJ. Genetic influences in gastro-oesophageal reflux disease: a twin study. Gut. 2003;52:1085–9.
9. Lembo A, Zaman M, Jones M, Talley NJ. Influence of genetics on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: a twin study. Aliment Pharmacol Ther. 2007;25:1343–50.
10. Uday C. Ghoshal & Dipti Chourasia Genetic factors in the pathogenesis of gastroesophageal reflux disease Indian J Gastroenterol. 2011;30(2):55–62. DOI: 10.1007/s12664-011-0095-7.
11. Heidi E. Hamm The Many Faces of G Protein Signaling The Journal of Biological Chemistry. 1998 January 9;273:669–672. DOI: 10.1074/jbc.273.2.669.
12. Siffert W, Rosskopf D, Siffert G et al. Association of a human G-protein beta3 subunit variant with hypertension. Nat Genet. 1998;18:45–8.
13. Rosskopf D, Manthey I, Habich Cet al. Identification and characterization of G beta 3s2, a novel splice variant of the G-protein beta 3 subunit. Biochem J. 2003 Apr 1;371:223–32. DOI: 10.1042/bj20021208.
14. Virchow S, Ansorge N, Ru¨ bben H, Siffert G, and Siffert W. Enhanced fMLP-stimulated chemotaxis in human neutrophils from individuals carrying the G protein 3 subunit 825 T-allele. FEBS Lett. 1998;436:155–158.
15. Lindemann M, Virchow S, Ramann F, Barsegian V, Kreuzfelder E, Siffert W, Müller N, and Grosse-Wilde H. The G protein β3 subunit 825T allele is a genetic marker for enhanced T cell response. FEBS Lett. 2001;495:82–86.
16. de Vries DR, ter Linde JJ, van Herwaarden MA, Smout AJ, Samsom M. Gastroesophageal reflux disease is associated with the C825T polymorphism in the G-protein beta3 subunit gene (GNB3). Am J Gastroenterol. 2009;104:281–5.
17. Lee HJ, Cha JH, Ham BJ et al. Association between a G-protein β3 sub-unit gene polymorphism and the symptomatology and treatment responses of major depressive disorders. Pharmacogenomics J. 2004;4:29–33.
18. Siffert W, Forster P, Jöckel KH et al.Worldwide ethnic distribution of the G protein beta3 subunit 825T allele and its association with obesity in Caucasian, Chinese, and Black African individuals. J Am Soc Nephrol. 1999 Sep;10:1921–30.
19. Hauner H, Meier M, Jöckel KH, Frey UH, Siffert W. Prediction of successful weight reduction under sibutramine therapy through genotyping of the G-protein beta3 subunit gene (GNB3) C825T polymorphism. Pharmacogenetics. 2003 Aug;13(8):453-9.
20. Park YM, Chung YC, Lee SH et al. G-protein b3 subunit gene 825C/T polymorphism is not associated with olanzapine-induced weight gain in Korean schizophrenic patients. Psychiatry Investig. 2009;6:39–43.
21. Rosskopf D, Manthey I, Siffert W. Identification and ethnic distribution of major haplotypes in the gene GNB3 encoding the G-protein beta3 subunit. Pharmacogenetics. 2002;12:209–20.
22. Tahara T, Arisawa T, Shibata T et al. Homozygous 825T allele of the GNB3 protein influences the susceptibility of Japanese to dyspepsia. Dig Dis Sci. 2008;53:642–6.
23. Holtmann G, Siffert W, Haag S et al. G-protein b3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. Gastroenterology. 2004;126:971–9.
24. Lee H-j, Lee S-y, Choi JE, Kim JH, Sung I-k, Park HS, Jin CJ. G protein β3 subunit, interleukin-10, and tumor necrosis factor-α gene polymorphisms in Koreans with irritable bowel syndrome. Neurogastroenterology & Motility. 2010;22:758–763. DOI: 10.1111/j.1365-2982.2010.01496.x
25. Oshima T, Nakajima S, Yokoyama T, Toyoshima F, Sakurai J, Tanaka J, Tomita T, Kim Y, Hori K, Matsumoto T, Miwa H. The G-Protein β3 subunit 825 TT genotype is associated with epigastric pain syndrome-like dyspepsia. BMC Med Genet. 2010;11:13. DOI: 10.1186/1471-2350-11-13.
26. Gutersohn A, Naber C, Müller N, Erbel R, and Siffert W. G protein β3 subunit 825 TT genotype and post-pregnancy weight retention. Lancet. 2000;355:1240–1241.
27. Hengstenberg C, Schunkert H, Mayer B, Döring A, Löwel H, Hense H, Fischer M, Riegger GA, and Holmer SR. Association between a polymorphism in the G protein β3 subunit gene (GNB3) with arterial hypertension but not with myocardial infarction. Cardiovasc Res. 2001;49:820–827.
28. Winfried Siffert Effects of the G protein β3-subunit gene C825T polymorphism: should hypotheses regarding the molecular mechanisms underlying enhanced G protein activation be revised? Focus on "A splice variant of the G protein β3-subunit implicated in disease states does not modulate ion channels". Physiological Genomics. 2003;2(13):81–84 DOI: 10.1152/physiolgenomics.00031.2003.
29. Ruiz-Velasco V and Ikeda SR. A splice variant of the G protein β3-subunit implicated in disease states does not modulate ion channels. Physiol Genomics. 2003;13:85–95.

Acceptance for editing: 2017-08-15
Acceptance for publication: 2017-09-30

Correspondence address:
Marta Dats-Opoka
Department of Propedeutics of Pediatrics
and Medical Genetics
Danylo Halytsky Lviv National Medical University
69 Pekarska Street, Lviv, Ukraine, 79010
email: martadats@gmail.com