hepatocyte nuclear factor-4alpha // J Mol Endocrinol. 2009; 43(1):19–27. Doi: 10.1677/JME-09-0025

37. The association between subclinical hypothyroidism and erectile dysfunction / Chen D, Yan Y, Huang H. [et al.] // Pak J Med Sci. 2018; 34(3):621–5. Doi:10.12669/pjms.343.14330

38. The influence of hyperthyroidism on the hypothalamic-pituitary-gonadal axis / Zähringer S, Tomova A, von Werder K. [et al.] // Exp Clin Endocrinol Diabetes. 2000; 108(4):282–9. Doi: 10.1055/s-2000-7756

39. The role of hypothyroidism in male infertility and erectile dysfunction / Nikoobakht MR, Aloosh M, Nikoobakht N. [et al.] // Urol J. 2012; 9(1):405–9.

40. The type 3 deiodinase is a critical determinant of appropriate thyroid hormone action in the developing testis / Martinez ME, Karaczyn A, Stohn JP. [et al.] // Endocrinology. 2016; 157(3):1276–88. Doi: 10.1210/en.2015-1910

41. Thyroid hormones, Sertoli cell proliferation and differentiation in progenies from carbamazepine-treated rat dams during pregnancy and lactation / Oliva SU, Andretta RR, Simas JN. [et al.] // Andrologia. 2021; 53(3):e13969. Doi: 10.1111/and.13969

42. Transient hypothyroidism: dual effect on adult-type Leydig cell and Sertoli cell development / Rijntjes E, Gomes MLM, Zupanič N. [et al.] // Front Physiol. 2017; 23(8):323. Doi: 10.3389/fphys.2017.00323

43. Type 2 iodothyronine deiodinase is highly expressed in germ cells of adult rat testis / Wajner SM, dos Santos Wagner M, Melo RC. [et al.] // J Endocrinol. 2007; 194(1):47–54. Doi: 10.1677/JOE-07-0106

44. Wagner MS, Wajner SM, Maia AL. The role of thyroid hormone in testicular development and function // J Endocrinol. 2008; 199(3):351–65. Doi: 10.1677/JOE-08-0218

45. Wajner SM, Wagner MS, Maia AL. Clinical implications of altered thyroid status in male testicular function // Arq Bras Endocrinol Metabol. 2009; 53(8):976–82. Doi: 10.1590/s0004-27302009000800011

46. Winters SJ. SHBG and total testosterone levels in men with adult onset hypogonadism: what are we overlooking? // Clin Diabetes Endocrinol. 2020; 6:17. Doi: 10.1186/s40842-020-00106-3

Yu.R. Sagadatova, A.G.Khasanov, I.R. Gilyazova, A.F. Badretdinov, R.R. Fayazov, I.F. Sufiyarov

DOI 10.25789/YMJ.2022.77.27

УДК 575.1:616.33

GENES-MARKERS OF PEPTIC ULCER DISEASE

The review presents the analysis of the literature on genetic studies devoted to candidate genes for peptic ulcer disease. All the materials of these publications can be combined into two large groups: studies devoted to investigation of peptic ulcer inducer genes and studies devoted to protective genes. The main groups of ulcer inducer genes (*ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFα, TGF-b1, B1,2,3, CYP2C19, MMP-2, MMP-3, MMP-9, Toll,TLR4TLR9, MIF, MPO*) and protectors (*IL-1, IL-1RN, TNF, LTA, IL-1b, MMP-3*) were identified, but most of the results obtained to date are inconsistent, poorly reproduced in ethnically diverse populations, which makes it relevant to study this problem among different groups living in the Russian Federation.

Keywords: Peptic ulcer in women, peptic ulcer of the stomach and duodenum, genes, genes-markers of peptic ulcer disease, literature review.

Introduction. According to the world statistics, the prevalence of gastroduodenal ulcer is 5-15% of the world population [25]. Moreover, ulcer disease with localization in the duodenum is 4-13 times more common than gastric ulcers. Currently, there is an increase in the number of ulcer disease among women. The ratio of men and women in the incidence of duodenal ulcer is 1,9 : 1 in the USA, 2,2 : 1 in Europe and 3,6 : 1 in China. However, complicated forms ulcer diseases in women are observed 2-4 times less frequently than in men. Conspicuous is the fact that the highest incidence of Ulcer Disease in men is in their 20s with a gradual decrease by the age of 40 [8]. In women, the incidence rate is, on the contrary, higher with increasing age of the pathology [2].

It is commonly known that ulcerative defect of the mucous membrane of the stomach and duodenum occurs due to the predominance of aggression factors over protection factors. Nevertheless, later, during years of research, scientists discovered a bacterium unknown at that time, which was named H. pylori [2]. The microorganism was first isolated in 1982 by B. Marshall and R. Warren. They showed by their own example that this bacterium plays a fundamental role in the formation of gastric mucosa ulcers. Despite the fact that the cause of ulcers was "established" and experimentally proved, however, the question of differences in the frequency of ulcers in this or that category of people was still open. In addition to the infectious theory, inflammatory, gastric, peptic, vascular, spastic, mechanical, neurotrophic and cortico-visceral theories were considered as the ultimate cause of ulceration. However, none of these theories could explain the true nature of the ulcer. The question of Crouvellier (1835), "why does an ulcer arise in one place, while the rest of the mucosa remains intact," is still relevant today.

The possibility of determining disposition towards many multifactorial diseases has become a reality due to the development of molecular genetics. The results of treatment of these diseases can be determined by a specific set of polymorphic gene variants. The study of the genetic basis of these diseases allows not only to predict the course of the disease, but also prevents the occurrence of complications. Some genetic markers, such as blood group O (*ABO* gene, rs505922) [22], asecretory status, hyperpepsinogenemia (I/D)[19] and HLA antigens, polymorphic loci of the *PSCA* gene (prostate stem cell antigen, rs2294008) [19] have been described as associated with ulcer disease, although so far the results have been contradictory.

Due to the increasing incidence of ulcer disease and the frequent development of complications, the study of genes involved in the formation of ulcer disease is an extremely important task, the solu-

SAGADATOVA Yuliya Riyazovna – Postgraduate student of the Department of Surgical Diseases, orcid.org/0000- 0002-2922-7087; **KHASANOV Anvar Giniyatovich** – Doctor of Medical Sciences, Professor, Head of the Department of Surgical Diseases, orcid.org/0000- 0001-5870-8894, **GILYAZOVA Irina Rishatovna** – Candidate of Biological Sciences, Associate Professor of the Department of Medical Genetics and Fundamental Medicine of IDPO, senior research fellow, orcid.org/0000-0001-9499-56322; **BADRETDINOV Azamat Fuatovich** – Candidate of Medical Sciences, Associate Professor of the Department of Surgical Diseases, orcid.org/0000-0003-2738-393X; **FAYAZOV Radik Radifovich** – Doctor of Medical Sciences, Professor of the Department of Surgical Diseases, orcid.org/0000-0003-1890-2865; **SUFIYAROV Ildar Fanusovich** – Doctor of Medical Sciences, Professor of the Department of Surgical Diseases, Dean of the Faculty of Pediatrics, orcid.org/0000- 0001-8688-8458

tion of which will allow to formulate more accurate ideas about the pathogenesis of the disease.

The object of this research paper is to summarize the literature data on the results of genetic studies on ulcer disease and their subsequent systematization.

Discussion. Over the past decade, about 50 scientific studies have been conducted on various genes that cause pathology of the gastrointestinal tract, including gastric and duodenal ulcers. The analysis of both foreign and Russian literature on this topic showed that the most part of publications contains information on the study of gene polymorphism mainly from the point of view of oncological predisposition. All the materials of these published articles can be combined into two large groups: studies devoted to ulcer inducer genes and studies devoted to protector genes.

Ulceration inducer genes. Currently, there are several dozens of candidate genes for ulcer disease: *ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFa, TGF-b1, MMP, Toll, TLR4TLR9, MIF, MPO*.

It is known that the ability of the immune system to adequately respond to the existing pathological factors directly depends on the genetic structure of the microorganism. Cytokines, a group of polypeptide mediators, are of great importance in maintaining the body balance. They include interferons, colony-stimulating factors, interleukins, chemokines, transforming growth factors, a group of tumor necrosis factor and others [21]. With the help of blood cells, endothelium, connective tissue and epithelial cells, cytokines regulate the adequate response of local protective factors of the body to the effects of foreign agents. It is revealed that disturbance of cytokine synthesis, through cell damage, leads to the development of chronic gastroduodenal diseases. Particularly, a high level of cytokines leads to the activation of matrix metalloproteases and collagenases, which leads to increased destruction of carbohydrate-protein components of the connective tissue. Cytokine genes have a high degree of polymorphism. Cytokines possess the ability to activate and suppress themselves, other cytokines and their receptors, participating in the formation of a cytokine network. Genes encoding pro-inflammatory (IL-1, IL-6, IL-8, TNF-a) and anti-inflammatory cytokines (IL-10) directly affect the value of the cytokine response.

Interleukin -1B (IL-1B). As mentioned above, cytokines are actively involved in the body's defense against foreign agents. Such an agent in ulcer disease is mostly H. pylori. In response to H. pylori infection, the body reacts in the form of a sharp release of pro-inflammatory cytokines. Yet, if a macro organism has one of the polymorphic variants of the *IL-1B* gene (homo- or heterozygous for the high-producing allele), cytokine release occurs 2-4 times stronger than in ordinary people. IL-1ß is also one of the most powerful inhibitors of hydrochloric acid secretion - by 100 times stronger than proton pump inhibitors, and 6000 times stronger than H2 receptor antagonists. A less percentage of cytokines in the body potentiate an even greater inhibition of acid production of the gastric mucosa and the expansion of H. pylori colonization with the further development of inflammatory changes. In the longer term low acid production forms atrophy of the gastric mucosa. Some studies have shown that individuals with a combination of *IL-1B*-511*T and *IL-1B*-31*C or *IL-1RN* *2/*2 (2 repeats of 86 BP) which are classified as high - producing alleles are more vulnerable to the development of gastric atrophy, gastroduodenal ulcers and gastric cancer than those with the *IL-1B*-511*C, *IL-1B*-31*T or *IL-1RN**2 alleles [27,30]. But according to the results of a research study of children by Chinese scientists, no association was found between *IL-1* polymorphisms and H. pylori infection or gastric mucosal *IL-1* expression levels. Mostly, people (60.7%) with moderate or severe gastritis (stomach ulcer) had *IL-1B*-511TT/-31CC [27].

A research devoted to the study of polymorphic variants of *IL1ß* genes (interleukin 1-beta) (3953C>T, rs1143634), >*IL1RN*(receptor antagonist of interleukin 1) (VNTR, rs71941886), *IL8*(-251T>A, rs4073), >*IL10*(–627C>A, rs1800872) and >*TNFa* (–308G>A, rs1800629) in patients with gastroduodenal ulcer was conducted in the Republic of Bashkortostan. An increased risk of developing Ulcer Disease was associated only with the C allele (OR=2.87, p=0.006) and the CC genotype (OR=4.49, p=0.002) of the polymorphic variant rs1143634 (+3953C>T) of the *IL1B* gene among Bashkirs [1].

Interleukin -6 (IL-6). Interleukin-6 is a bidirectional cytokine that is important in host defense as an intermediary between innate and acquired immune systems, stimulating the production of IFN-γ, differentiation and maintenance of cytotoxic T cells, as well as promoting the secretion of immunoglobulin in activated B cells [7]. The levels of IL-6 in the gastric mucosa increase with associated gastritis and decrease after the infection is eliminated [27]. There were identified three polymorphisms of *IL-6* genes, which are located on chromosome 7p21, *IL-6*–174, -572 - [7]. It was revealed that *IL-6*-174 G and *IL-6*-572GG produce higher levels of IL-6 than carriers of the C/C genotype [28]. However, the connection between this polymorphism and Ulcer Disease remains unclear. The study reported that the frequencies of the *IL-6*–572 G/G genotype (P = 0.027) and the *IL-6*–572 G allele were lower in H. pylori-positive patients (P = 0.003) [27]. Moreover, the risk of gastric ulcer was significantly higher in carriers of the G/G genotype (OR= 58.86) and the G allele (OR = 33.10).

Interleukin-8 (IL-8). Interleukin - 8 is a pro-inflammatory cytokine that plays a significant role in the pathogenesis of acquired diseases. High production of interleukin-8 was detected in gastric epithelial cells during infection caused by the cag-PAI-positive strain of H. pylori. It is essential to the initiation, modulation and sustentation of inflammatory reactions of the gastrointestinal tract. High levels of IL-8 can increase the inflammatory response to H. pylori by activating neutrophils and monocytes, which leads to the formation of gastritis [28]. There are three polymorphic variants in the *IL-8* gene associated high produce of this protein: - A/T, - T/G and - C/T . The common single nucleotide polymorphism (SNP) at position -10 is associated with increased IL-8 production. The *T-to-A* mutation can affect the transcription and secretion of IL-8 [18].

Some research shown association between polymorph variants of *IL-8* and peptic ulcer disease. So, it was shown that H. pylori-positive patients with genotype A/A of the *IL-8* gene have an increased risk of developing Ulcer Disease (OR = 2.08) [17]. Similar results were obtained in a study of colleagues from Europe and Korea [24]. Among the Japanese population, the *IL-8*–251 A/A genotype is associated with a higher risk of developing Gastric Ulcer (OR 2.07) than the T/T genotype. Severe gastric atrophy is also significantly more common in the groups of patients carrying the A/A or A/T genotypes than in the group of patients carrying the T/T genotype [18].

Interleukin-10 (IL-10). Interleukin - 10 is an anti-inflammatory cytokine that suppresses the synthesis of IL-1B, TNF-α, interferon-γ and other pro-inflammatory cytokines. The effects of IL-10 on other cell types include inhibition of pro-inflammatory cytokine production by activated monocytes/macrophages. A relative deficiency of IL-10 can lead to a Th-1-induced hyper-inflammatory reaction

to H. pylori with progressive damage to the gastric mucosa. H. pylori can lead to an increase in IL-10 and suppression of the immune response, which contributes to the survival of bacteria [27]. Analyzing the *IL-10* gene, L.V. Volevach and L.V. Gabbasova found out that the genotype rs1800872*AA and the allele rs1800872*A of the *IL10* gene (-627C>A; rs1800872), p=0.017, OR=0.091 (CI95% (0.011-0.751) and p=0.025, OR=0.544 (CI95% (0.329-0.902)) are accompanied by a high risk of duodenal ulcers among Tatars [4]. Duodenal ulcer with a burdened hereditary history (rs1800872*AA and rs1800872*A) is characterized by a more severe clinical picture (pain syndrome) (84.72 ± 4.24%), progressive course with frequent annual exacerbations (more than 2-3 times a year in 72.22± 5.28%), high risk of complications (13.89).

TNF-a. Tumor necrosis factor (*TNF*) is a gene that encodes a multifunctional cytokine formed mainly by monocytes and macrophages. Present studies showed that among the five biallelic polymorphisms in the *TNF-A* promoter region, *TNF-A*-238 G/A and -308 G/A polymorphisms are associated with a high risk of ulcer disease [9]. Both-1031C and -863A have been found to be independent risk factors for the development of gastric and duodenal ulcers without intestinal metaplasia among people infected with H. pylori [18].

TGF-beta1. Transforming Growth Factor-beta1 (TGF-beta1) is an important cytokine that plays a role in cell proliferation, differentiation, tissue injury repair and ulcer healing. A research study by Russian scientists [6] in 2006 revealed that the combination of 10L/L25R/R-509C/C is more common in the group of patients with gastric ulcer, and the combination of 10P/P25R/P-509C/T is more common in patients with duodenal pathology.

Matrix metalloproteinases. Matrix metalloproteinases are a family of extracellular zinc-dependent endopeptidases capable of cleaving extracellular matrix components. They are involved in tissue remodeling, angiogenesis, cell proliferation, migration and differentiation, apoptosis, and inhibition of tumor growth. It is known that the presence of H. pylori infection increases the activity of MMP-2 and MMP-9, which are involved in the processes of tissue destruction.

The study of the polymorphic variant -468G/A of the *MPO* (myeloperoxidase) gene was carried out among the population of the island of Taiwan. The study included 115 patients with Duodenal Ulcer and 182 healthy people. The association of the allele A of the *MPO* gene with the development of the disease (OR=2.3, p=0.008) was established.

Toll-like receptor genes. The more active studied *Toll*-like receptor include polymorphisms *TLR4*+896A/G (rs4986790) and +1196C/T (rs4986791).

So, scientists from Iran also investigated single nucleotide gene substitutions of *Toll*-like receptors of type 4 *TLR4*+896A/G (rs4986790) (Asp299Gly), +1196C/T (rs4986791) (thr399ile) and +3725G/C (rs11536889). It was revealed that UD develops in carriers of CT+TT genotypes (rs4986791).

According to other authors, the risk of developing Duodenal Ulcer is associated with polymorphism of another gene of signaling peptides: *TLR9*+2848G>A (rs352140). The rs352140 A allele is associated with an increased risk of developing Duodenal Ulcer (OR=2.13, p=0.04) [11].

Genes of digestive enzymes. The role of hyperpepsinogenemia in the development of ulcer disease has been known for a long time. However, only in the second half of the 20th century, the American gastroenterologist M. Samloff found out that the concentration of pepsin proenzymes in blood serum is associated with the level of acid production of the stomach. [24].

Genes - protectors of the UD development. By reviewing the literature, we found that there are fewer works devoted to the study of "protective" genes. This circumstance is likely to be related to the difficulties in the selecting material for the study. There can be distinguished the following protectors of ulcer disease: *IL-1, IL-1RN, MMP-3.*

The scientist study [14] notice IL-1B and IL-1RN as an independent protective factor in duodenal ulcer. The explanation of this discovery may suggest that the carrier of these polymorphisms was associated with high production of IL-1b, which, due to its inhibitory effect of acid on the stomach, can reduce the risk of developing duodenal ulcer. However, it may increase the risk of developing gastric cancer. A study by E. Shaymardanova (2014) showed that the T allele (rs1143634) of *IL-1B* gene plays a protective role in the development of Ulcer Disease (OR=0.35, p=0.006) [6].

The genes of matrix metalloproteinases, in particular stromelysin-1 (*MMP-3*), are also considered as protective genes. Elevated levels of MMP-3 are recorded in patients with Gastric Ulcer. This endopeptidase is thought to play a protective role [2,16]. Another study suggests that melatonin suppresses the synthesis of MMP, leading to the healing of ulcers [16].

Conclusion. Summarizing all the information, we can say that the genetic basis of ulcer disease has not been studied enough. The main groups of ulcer inducer genes (*ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFα, TGF-b1, MMP, Toll, TLR4TLR9, MPO*) and protectors (*IL-1, IL-1RN, MMP-3*) were identified, but most of the results obtained to date are inconsistent, poorly reproduced in ethnically diverse populations, which makes it relevant to study this problem among different groups living in the Russian Federation.

Reference

1. Nurgalieva AH, Shaimardanova EH, Hidiyatova IM [et al.] Associacii polimorfny`x variantov genov citokinov s riskom razvitiya yazvennoj bolezni v respublike Bashkortostan [Associations of polymorphic variants of cytokine genes with the risk of developing peptic ulcer disease in the Republic of Bashkortostan]. Genetics. 2014; 50 (12): 1455 (In Russ.).
2. Valova, Y.V. Faktory` riska razvitiya yazvennoj bolezni. Aktual`ny`e voprosy` e`kologii cheloveka [Risk factors in the development of ulcer disease. Topical issues of human ecology]. Sbornik nauchny`x statej uchastnikov Vserossijskoj nauchno-prakticheskoj konferencii s mezhdunarodny`m uchastiem: v 3-x tomax [Collection of scientific articles of participants of the All-Russian Scientific and practical conference with international participation: in 3 volumes]. 2015; 41-46 (In Russ.).
3. Sadykova, KG, Rakhimbekov BG. Geneticheskie prediktory` oslozhnennogo techeniya yazvennoj bolezni [Genetic predictors of the complicated course of peptic ulcer disease]. Internauka. 2020; 19: 1(148): 65-66 (In Russ).
4. Volevach LV, Gabbasova LV, Kuramshina OA [et al.]. Kharakteristika nasledstvennoj predraspolozhennosti pri yazvennoj bolezni dvenadczatiperstnoj kishki [Characteristics of hereditary predisposition in duodenal ulcer]. Sovremeny`e problemy` nauki i obrazovaniya [Modern problems of science and education]. 2017; 5 (In Russ.).
5. Sagadatova YuR, Khasanov AG, Sufiyarov IF [et al.]. Yazvennaya bolezn` u zhenshhin. [Pulcer disease in women]. Experimental and Clinical Gastroenterology [E`ksperimental`naya i klinicheskaya gastroe`nterologiya]. 2021 (8): 160-166 (In Russ.). Doi: 10.31146/1682-8658-ecg-192-8-160-166.
6. Yariev AA, Karimov HYa, Babaev AT. Polimorfizm RS1800471 gena TGFB1 v formirovanii predraspolozhennosti k yazvennoj bolezni dvenadczatiperstnoj kishki i xronicheskogo gastrita [Polymorphism RS1800471 of the TGFB1 gene in the formation of predisposition to duodenal ulcer and chronic gastritis]. Vestnik neotlozhnoj i vosstanovitel`noj xirurgii [Bulletin of Emergency and Reconstructive Surgery]. 2018; 3 (3): 289-297 (In Russ.).
7. Chauhan P, Nair A, Patidar A [et al.] A primer on cytokines. Cytokine. 2021;145:155458. DOI: 10.1016/j.cyto.2021.155458
8. Moayyedi P, Lacy BE, Andrews SN [et al.] American College of Gastroenterology and Canadian Association of Gastroenterology guidelines on the management of dyspepsia. Am J Gas-

troenterol. 2017; 112: 988–1013. DOI: 10.1038/ajg.2017.154

9. Zhao H, Liu L, Liu B, [et al.]. An updated association between TNF-α-238G/A polymorphism and gastric cancer susceptibility in East Asians. Bioscience reports. 2018; 38 (3). BSR20181231 DOI: 10.1042/BSR20181231

10. Ren HY, Wen LS, Geng YH [et al.] Association between IL-1B gene polymorphisms and Helicobacter pylori infection: a meta-analysis. Microbial pathogenesis. 2019; 137: 103769. DOI: 10.1016/j.micpath.2019.103769

11. Mirkamandar E, Nemati M, Hayatbakhsh M [et al.]. Association of a single nucleotide polymorphism in the TLR2 gene (rs3804099), but not in the TLR4 gene (rs4986790), with Helicobacter pyloriinfection and peptic ulcer. The Turkish Journal of Gastroenterology. 2018; 29(3): 283–291. DOI: 10.5152/tjg.2018.17484

12. Tourani M, Habibzadeh M, Shokri-Shirvani J [et al.] Association of Helicobacter pyloriinfection with Toll-like receptor-4 Th r399Ile polymorphism increased the risk of peptic ulcer development in North of Iran. Journal of Pathology, Microbiology and Immunology. 2017; 126 (1): 76–84. DOI: 10.1111/apm.12779

13. Khatoon, J., Prasad, K. N., Prakash Rai [et al.] Association of heterogenicity of Helicobacter pylori cag pathogenicity island with peptic ulcer diseases and gastric cancer. British journal of biomedical science. 2017; 74 (3): 121-126.

14. Motamedi RN, Rezaeishahmirzadi M, Shakeri S [et al.]. Association of IL-1B+3954 and IL-1RN Polymorphisms in Chronic Gastritis and Peptic Ulcer. Iran J Public Health. 2018; 47 (9): 1364-1370.

15. Zhang J, Sun X, Wang J, [et al.]. Association of the IL-1RN variable number of tandem repeat polymorphism and Helicobacter pylori infection: A meta-analysis. PloS one. 2017; 12(4): e0175052. DOI: 10.1371/journal.pone.0175052

16. Bagheri N, Sadeghiani M, Rahimian G [et al]. Correlation between expression of MMP-9 and MMP-3 in Helicobacter pylori infected patients with different gastroduodenal diseases. Arab journal of gastroenterology. 2018; 19 (4): 148-154. DOI: 10.1016/j.ajg.2018.11.001

17. Frank S. A. Immunology and evolution of infectious disease. Princeton University Press. 2020. DOI: 10.1515/9780691220161

18. Gonzalez-Hormazabal P, Romero S, Musleh M [et al.] IL-8-251T> A (rs4073) polymorphism is associated with prognosis in gastric cancer patients. Anticancer research. 2018; 38 (10): 5703-5708. DOI: DOI: 10.21873/anticanres.12907

19. Usui Y, Matsuo K, Ozeet I [et al.] Impact of PSCA polymorphism on the risk of duodenal ulcer. Journal of epidemiology. 2019 DOI: 10.2188/jea.JE20190184 (65)

20. Barakat SH, Meheissen MA, El-Gendi SM [et al.]. Interleukin-1β and Interleukin-1 receptor antagonist gene polymorphism in pediatric patients with Helicobacter pylori-associated chronic gastritis. Journal of Tropical Pediatrics. 2021; 67 (3). DOI: 10.1093/tropej/fmab061

21. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. International journal of molecular sciences. 2019; 20 (3): 6008. DOI:10.3390/ijms20236008

22. Lanas A, Chan F. K.L. Peptic ulcer disease. The Lancet. 2017; 390 (10094): 613-624. DOI: 10.1016/S0140-6736(16)32404-7

23. Magris R, V. De Re, Maiero S [et al.] Low pepsinogen I/II ratio and high gastrin-17 levels typify chronic atrophic autoimmune gastritis patients with gastric neuroendocrine tumors. Clinical and Translational Gastroenterology. 2020; 11 (9). DOI: 10.14309/ctg.0000000000000238

24. Malfertheiner P, Megraud F, O'Morain C [et al.]Management of Helicobacter pylori infection–the Maastricht V. Florence Consensus. Report. 2017; 66(1): 6–30.

25. Miftahussurur M, Yamaoka Y. Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev Gastroenterol Hepatol. 2015; 9 (12): 1535-47. doi: 10.1586/17474124.2015.1095089.

26. Minyaylo O, Ponomarenko I, Reshetnicov E. Functionally significant polymorphisms of the MMP-9 gene are associated with peptic ulcer disease in the Caucasian population of Central Russia. Scientific reports. 2021; 11(1): 1-8.

27. Ramis IB, Vianna JS, Gonçalves CV [et al.]. Polymorphisms of the IL-6, IL-8 and IL-10 genes and the risk of gastric pathology in patients infected with Helicobacter pylori. Journal of Microbiology, Immunology and Infection. 2017; 50 (2): 153-159. DOI: 10.1016/j.jmii.2015.03.002

28. Essadik A, Jouhadi H, Rhouda T. Polymorphisms of Tumor Necrosis Factor Alpha in Moroccan Patients with Gastric Pathology: New Single- Nucleotide Polymorphisms in TNF-α (–193) (G/A). Mediators of Inflammation. 2015; 143941. DOI: 10.1155/2015/143941.

29. Cho J.H., Choi J. S., Chun S.W. The IL-1B genetic polymorphism is associated with aspirin-induced Peptic Ulcers in a Korean Ethnic Group. Gut and Liver. 2016; 10 (3): 362.

30. Zeyaullah M, AlShahrani MA, Ahmad I. Association of Helicobacter pylori Infection and Host Cytokine Gene Polymorphism with Gastric Cancer. Canadian Journal of Gastroenterology and Hepatology. 2021. DOI: 10.1155/2021/8810620