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Helicobacter pylori Genotype as Predicts Risk of (Ulcer Disease, Gastric Cancer, Non-Ulcer Dyspepsia); Role of some genes Mediated Signaling in infection

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Abstract

Helicobacter pylori contagion is magnanimously overruling in human, disturbance privately partial of the world's population; reciprocally, contagion continue asymptomatic in superiority of population. During its co-existence with humans, H. pylori has develop diversified strategies to preserver a kind gastritis and edge the protected response of host. On the other side, personality of H. pylori is also combined with increased exposure for the evolution of uncertain gastric pathologies conclude gastric malignancy (GC).

A complicate confederacy of host genetics, environmental agents, and bacterial virulence agent are estimate to regulate the capability as well as the extremity of consequence in a subset of individuals. The nearness of the babA2 quality was altogether joined with the various H pylori destructiveness qualities planned (vacA, cagA, and homB). High and significant results was belong to vacA in Peptic Ulcer Disease (91.04%), homB in Gastric Cancer (93.51%) and babA2 in Non-Ulcer Dyspepsia

Keywords: *Helicobacter pylori*, vacA, cagA, and homB, Peptic Ulcer Disease, Gastric Cancer, Non-Ulcer Dyspepsia

INTRODUCTION

More than 70% of all major malignances befall to the liver Hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA) and gastric cancer [1]. These developments rank third among organ-particular wellspring of damage related passings in men boundless and depiction for practically 4% of each and every human tumor. The geographic regions most associated are placed in Southeast Asia particularly in Thailand. Steady hepatitis B contamination (HBV) and hepatitis C disease (HCV) malady and aflatoxins are the principle reason of HCC [2]. H pylori can be chracterize in maintain; it is contemplate microaerophilic gram-negative bacterium which gifted to settle and carry on within the stratum of mucous membrane in gastric [3]. Numerous revisions describe a contiguous union between infection by H pylori and diseases of gastroduodenal, for application MALT-lymphoma, PUD, GC and continuing sprightly gastritis [4]. The quarter most frequent universal malignancy was GC and observe as secondary guidance reason of neoplasia-related deaths (more than half million deaths annually) [5].

H. pylori influence amenable for 60% of all chronic GC [6], contagion with that bacterium operate a fundamental role, hereditary and environmental element adjust its consequence. Tries have offer that disinfecting of this bacterium may diminish the risk of malignant infection, however overhaul the shot of gastro-esophageal response (GERD), Barrett's throat, and esophageal adenocarcinoma. Considering the centrality of H pylori in clear wreckage heaps, it is major to see which get-together of H pylori have the initiating to improvement the introduction of GC and PUD [7,8].

Inflammatory reaction heart by H. pylori that settle in stomach capable to clear gastritis "a gastric mucosal condition" among people and tentatively wiped out creatures. At the point when standard in the stomach, the microscopic organisms and gastric incitement can continue for some times of years in the lack of understanding cure. Late examination specify that unique indubitable varieties in a stepwise seek after of histological variations initiated by gastritis and that can at last impeccable in gastric harm; turbulence, gastric decay (privation of particularize cell speak to, for example, parietal cells and fundamental cells), intestinal metaplasia (character of intestinal-style epithelial tissue in the stomach), and dysplasia [9, 10].

The expansion of gastric neoplasia in the position of H. pylori proposition is beginning to be an entire arrangement result of a couple of changes, contain ceaseless turbulence (distinctive style of danger) [11], strengthening of gastric foundational microorganisms, DNA hurt, upgrade in cell duplication and apoptosis, substitute in epithelial division and most remote point, bringing down of neoplasm silencers, and diminishing gastric developing, course to bacterial hyperplasia with mix not found in the standard acidic stomach [12]. Outline of H. pylori and E.coli delineate it as great of intraspecies acquired refinement [13,14]. Nucleotide result masterminded combination of withdrew capable chief is chargeable to an incomprehensible change rate, other than a complimented recombination level of intraspecies [15,16].

Vacuolating cytotoxin A (vacA) a huge piece of the time impact in each H pylori age (Cover et al., 1994). Variety in sensible of cytotoxicity is trademark to vacA allelic change among H pylori strain, which surrender in the understanding (s), focus (m) and delegate (I) districts, each with two separate alleles: s1 or s2, m1 or m2 and 1i or i2, sensibly [17].

VacA was on an outstandingly major level clear sustained on its occupation to source vacuolation of epithelial cells however is after a short time reviving to have a basically more wide unique of activities [18-20]. The amino ruinous strategy, plan, and cell sign of VacA are disseated to those of some other expected bacterial harmful substances. Most VacA-induced cell changes are inferable from its ability for pore development in cell layers [21]. The clinical result of H. pylori tainting has been joined with bacterial deadly quality expert, have, and trademark constituent [22].

Two destructiveness variables of H. pylori, cytotoxin-going with quality A (cagA quality) and the vacuolating cytotoxin A quality (vacA quality), carry on a leader party in control the clinical impact of H. pylori pandemic. The cagA quality, the primary harmfulness specialist blame in H. pylori family, encodes a protein (CagA protein) that is going with expanded genuineness of gastric turbulence and substantial neutrophil granulocyte penetration [23]. In limb, the CagA protein generally actuates interleukin-8 (IL8) which assumes a meeting part in the rebellious cell reaction to virus 24. The cagA quality, which isn't moment in each H. pylori strain, examine a marker for a genomic pathogenicity island (cag-PAI). It examine that this quality with

others on the island correlative with more grim clinical results, contain PUD and gastric threat (GC) [24-27].

Advantageous settling in the stomach is the most expansive progression for the pathogenicity of H. pylori recommendation. It is thoroughly value that bacterial association with the gastric epithelial tissue is the central unforgiving level of settlement by H. pylori [28]. The blood mean antigen astringent adhesin (BabA) is a well-chracterize outside part protein of H. pylori that check fucosylated Lewisb blood add up to antigens minute on gastric epithelial tissue [29, 30]. Three bab allelic address have been seen, piece babA1, babA2 and babB; regardless, just the execution of the babA2 quality is changed for blessing the unassuming life plots with Lewisb astringent deftness. In 1999, Gerhard et al 31 first blueprint a without question connection between a babA2-quality real age and duodenal ulcer (DU) and GC. In this manner, a progression of thought of the connection between babA2 quality and PUD and GC have been done, however with conflicting or negating conclusions [32, 33].

In vitro, Helicobacter outside layer B (HomB) draw in the arrival of the proinflammatory cytokine interleukin-8 (IL-8) and improvement H. pylori's favorable position to interface with have cells [34]. All the more in a general sense, homB identity is on an extremely fundamental level running with disclosure of peptic ulcer issue in Portuguese relatives and junior grown-ups 35 and with gastric perniciousness change and the character of cagA in U.S. additionally, Colombian masses 36. These exposures propose that the outside film protein HomB is a pivotal risky quality authority.

Accordingly, it and unmistakable individuals from the frail paralogous get-together of hom simultaneousness particles are everything considered being survey. The two best-broke down hom qualities, homA and homB, are 90% dull at the nucleotide sensible. These homA and homB qualities can be writer at two unmistakable loci inside the H. pylori genome: region An and zone B. Strains can join an individual transcript of one of the hom properties, a twofold duplicate of an individual quality, a solitary transcript of every quality, or neither quality [35]. Past examination prescribe geographic social occasion, in either dispersals, zone, or transcript show up, of the hom attributes in the genome and impel that these standard blend impact any relationship with contamination result [37, 38].

MATERIALS & METHODS

Study location and subjects

From 471 cases in this study, only 194 adult patients (77; GC, 67; PUD, 50; NUD) were detected with H. pylori all of them was over 20 years, which referred to the Endoscopy section at Al-Hillah teaching Hospital Al-Hillah city, Iraq. Individuals who had received anti Helicobacter, anti-inflammatory medications or non-steroid treatment at least 100 days earlier to endoscopy was omitted [39].

Specimen Collection

For each patient endoscopy and biopsy sampling at least two biopsy specimens were obtained from the gastric antrum and examined for the presence of H. pylori by rapid-urease test, culture and histology examination, and an additional biopsy specimen (one antral biopsy specimen) from each patient was kept in brain heart infusion broth (Himedia, India) containing 20% glycerol for PCR analysis and frozen at -80°C until processing.

Blood samples.

Samples of blood was collected from all patients at the time of endoscopy. Sera were separated and stored at -80°C until tested for detection of the immunological criteria.

H. pylori Culture

Gastric biopsy specimens were standardized and cultivated on H. pylori selective media (Himedia, India). Cultivation of the streaking Petri dishes accomplished at 37°C for a week (under microaerophilic conditions) with in Co2 incubator (Binder, Germany). Documentation of H. pylori was constructed on macroscopic and microscopic characterization and complete by biochemical tests (positive oxidase, catalase, and urease tests) [40].

DNA Extraction and PCR for Detection of Gene

Extracted DNA from the isolated H. pylori strains in culture-positive cases and from gastric biopsy specimens done by using Promega kits by following the manufacture instruction.

In this study, genotyping of the selected gene (vacA, cagA, homB and babA2) that related to H pylori isolates were determined by PCR methods. PCR was carried out in an ultimate size of 20µl containing 13 µl of Taq PCR Master Mix (Biolab), 3 µl (10 µg/ µl) of extracted DNA, 2.0 µl (1 µM) of each primer. Amplification was performed with the following specific program for each primer.

Statistical Analysis

By using software of SPSS version 19, the data was analyzed. The Chi square (x2), and odds ratio (OR) were determined. A P-value less than or equal to 5% was considered as significant.

RESULTS & DISCUSSION

This study revealed the relation between the H. pylori infection and each types of gastroenteritis disease such as; PUD, GC and NUP. According to the data that collected from genetic, microbiology and histopathology tests, there are significant outcomes data that showed in table 2 and 3 below, which is clear the genes related to bacteria with the specific case (*vacA, cagA, homB and babA2* genes).

The proximity for babA2 quality was essentially running associate different H pylori danger characteristics organized (vacA, cagA, and homB). High and basic effect was interface with vacA in Peptic Ulcer Disease (91.04%), homB in Gastric Cancer (93.51%) and babA2 in Non-Ulcer Dyspepsia (100%). The full stipend was among man in all conditions as depict in table 2. We found basic relationship among babA2 and the other H pylori hurtfulness characteristics. These revelations are in congruity with those portray by various witness, similar to the essential relationship among cagA and the s1 and m1 alleles of vacA and oipA "on" [41, 42].

Table 1: primers of genes that selected in this research

Gene	Primer	Product
vacA	5'-ACTAATATTGGCACACTGGATTTG-3' 5'-CTCGCTTGATTGGACAGATTG-3'	298 bp
cagA	5'-AAT ACA CCA ACG CCT CCA AG-3' 5'-TTG TTG CCG CTT TTG CTC TC-3'	400 bp
homB	5'-AGAGGGTGTTTGAAACGCTCAATA-3' 5'-GGTGAATTCTTCTGCGGTTTG-3'	161 bp
babA2	5'-AAT CCA AAA AGG AGA AAA AGT ATG AAA -3' 5'-TGT TAG TGA TTT CGG TGT AGG ACA-3'	832bp

Table 2: Age and Gender relationship with each case groups studied

Criteria	Peptic Ulcer Disease		Gastric Cancer		Non-Ulcer Dyspepsia		P-value
	No	%	No	%	No	%	
Age (Mean ± SD)	46±7.8		48±3.9		42±8.2		P > 0.05
Gender:							
Male	46	68.7	53	68.8	39	78	P > 0.05
Female	21	31.3	24	31.2	11	22	P > 0.05
Total	67		77		50		

Table 3: Genes eminence among H. pylori-infected patients with each case groups studied.

Gene	Peptic Ulcer Disease (67)		Gastric Cancer (77)		Non-Ulcer Dyspepsia (50)		P-value
	No	%	No	%	No	%	
vacA	61	91.04	61	79.22	44	88	P > 0.05
cagA	54	80.60	70	90.91	42	84	P > 0.05
homB	42	62.69	72	93.51	47	94	P > 0.05
babA2	49	73.13	59	76.62	50	100	P > 0.05

cagA is put toward the entire of the cag pathogenicity island (PAI), which is a 39-kb put sequester on a level plane from another bacterial beginning stage. The "pathogenicity islands" contain cagA encode proteins conduce in sign transduction falls that follow in cytoskeletal change by strategies for actin polymerization and host cell protein phosphorylation. Risky social occasion of H. pylori accomplish the cagPAI. Inestimable. pylori race from patients with peptic ulcer or gastric peril create cagA, while colossal measures of those family from asymptomatically spread individuals deficiency this quality [43].Currently, we see two more discernible event of H. pylori specific: cagA quality pulverize and cagA quality positivestrains. Checking a stinging propensity virtuoso for cagA basically another chart that is kept up on polymorphism in Glu-Pro-Ile-Tyr-Ala (EPIYA) subjects. In cagA finish strains, there is an area join the EPIYA subjects, which encase a tyrosine phosphorylation put [44].

To now, vacA is the another most for the most part perscrutate hurting inclination ace of H. pylori. In each sensible recognize all H. pylori age have an ace vacA quality that codes for the cover pore-constraining protein vacA [45, 46]. The quality not too horrendous gathering in little living things passing on vacA is correspondence sensible and ailment control, which are joined with result change especially spaces of cover protein. There is a shocking break on our accessory concerning essential execution of this protein since still unique contradictive disclosures are exist [47, 48]. In this manner, we urgency more examination to control how to depend on vacA as serviceable H. pylori hurting penchant ace [49].

To conclusion, there have been distinctive reasonable contemplated yet with radiative effect on the relationship between the babA2 quality and PUD and GC [50]; additionally, there is no short meta-examination on the massiveness of babA2. As necessities be, we end up at ground zero the influenced metaanalysis to out of the helpful reveal learnedness to have a more right result. Another probability is that patients with enlarged gastritis in the corpus and antrum, stun diminished hazardous age, need to progress intestinal metaplasia, atrophic gastritis, and even GC [31]. It is hypothesis that babA2 confederated with different ruinous inclination ace may equivalently start to GC progress. Studies lead by Gerhard et al [52] and Erizin et al [51] have recommend that triple undeniable H. pylori family with cagA, vacAs1 and babA2 coexpression expand the threat of push GC. Zambon et al 53 have in like way relate that pollutions with these triple-positive race get a higher peril of intestinal metaplasia,known as gastric precancerous savagery.

In vitro, Helicobacter outside layer B (HomB) bolster the flooding of the proinflammatory cytokine interleukin-8 (IL-8) and make H. pylori's capacity to segment to have cells [34]. More essentially, homB closeness is all around joined with spreading out of peptic ulcer issue in Portuguese kids and vivacious adults [35] and with gastric risk loosening up and the district of cagA in U.S. besides, Colombian culture [36]. These disclosures suggest that the outside film protein HomB is another dangerous substance part. Along these lines, it and unmistakable people from the delicate paralogous family line of hom synchronization particles are generally speaking being perscrutate. The two best-dealt with hom characteristics, homA and homB, are 90% same at the nucleotide level [54]. These homA and homB characteristics can be unexpected at two separate loci inside the H. pylori genome: locus An and locus B. Strains can pass on a singular copy of one of the hom traits, a twofold copy of a specific quality, an uncompounded copy of each quality, or neither quality [15, 16]. Past reflection show geographic get-together, in either apportioning, condition, or duplicate wide number, of the hom characteristics in the genome and find that these particular blend master any association with warmth end [37].

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001; 94: 153-6.
2. Michielsen PP, Francque SM, van Dongen JL. Viral hepatitis and hepatocellular carcinoma. World J Surg Oncol 2005; 3: 27.
3. Atherton JC. The pathogenesis of Helicobacter pylori-induced gastro-duodenal diseases. Annu Rev Pathol, 2006;1: 63-96.
4. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med, 1991; 325: 1127-31.
5. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer, 2006; 118: 3030-44.
6. Peek RM, Jr, Fiske C, et al. Role of innate immunity in Helicobacter pylori-induced gastric malignancy. Physiol Rev, 2010; 90: 831-58.
7. Blaser MJ. Hypothesis: the changing relationships of Helicobacter pylori and humans: implications for health and disease.. J Infect Dis, 1999; 179: 1523-30.
8. Ali Hussein Al-Marzoqi, Ammal Ragib Shemran, Raad Abbas Kadhim, Zainab Haider Al-Mosawi, Lina Hassan Alasady, Worood Hamza Aldahmushe, Worood Alwan Al- Jeafry, Shahad Mohammed Darwal, Shahad Muhsen Hattem, Shahad Faddle Hashim. Genetic linked to leukemia: role of polymorphisms in candidate genes interconnected to leukemia. World Journal of Pharmaceutical Research. 2015; 4(5): 270-276.
9. Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer.. J Clin Invest 2007; 117: 60–69.
10. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer. 2013; 13:759 –771.
11. Cover TL, Blaser MJ. Helicobacter pylori in health and disease. Gastroenterology. 2009; 136:1863–1873.
12. Ali Hussein Al-Marzoqi, Nisreen Kaddim Radi, Ammal Raqib Shamran. Human genetic variation susceptibility associated with hbv: analysis of

genetic markers susceptibility to hepatitis b among patients in babylon province. World Journal of Pharmaceutical Research. 2015; 4(4): 102-113.
13. Suerbaum S, Josenhans C. Helicobacter pylori evolution and phenotypic diversification in a changing host. Nat Rev Microbiol 2007; 5: 441–452.
14. Morelli G, Didelot X, Kusecek B, Schwarz S, Bahlawane C, Falush D, Suerbaum S, Achtman M. Microevolution of Helicobacter pylori during prolonged infection of single hosts and within families. PLoS Genet 6:e1001036. 2010.
15. Olbermann P, Josenhans C, Moodley Y, Uhr M, Stamer C, Vauterin M, Suerbaum S, Achtman M, Linz B. A global overview of the genetic and functional diversity in the Helicobacter pylori cag pathogenicity island. PLoS Genet 6:e1001069. 2010.
16. Tasahel Hamid Al-Dulaimi, Hawraa Wahab Aziz, Ali Hussein Al-Marzoqi, Saad Abd Al-Aziz, Soad Abd Almahdi Mohsin Molecular Characterization and Antibiotic Susceptibility of Diarrheagenic. Escherichia coli from Children. Medical Journal of Babylon-2015; 12(2): 541-550.
17. Rhead JL, Letley DP, Mohammadi M., et al. A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. Gastroenterology, 2007;133: 926-36.
18. Cover TL, Blanke SR. Helicobacter pylori VacA, a paradigm for toxin multifunctionality. Nat Rev Microbiol 2005; 3: 320–332. http://dx.doi.org/10.1038/nrmicro1095.
19. Boquet P, Ricci V. Intoxication strategy of Helicobacter pylori VacA toxin. Trends Microbiol. 2012; 20:165–174.
20. Kim IJ, Blanke SR. Remodeling the host environment: modulation of the gastric epithelium by the Helicobacter pylori vacuolating toxin (VacA). Front Cell Infect Microbiol. 2012; 2:37.
21. Gangwer KA, Mushrush DJ, Stauff DL, Spiller B, McClain MS, Cover TL, Lacy DB. Crystal structure of the Helicobacter pylori Vacuolating toxin p55 domain. Proc Natl Acad SciUSA 2007;104:16293–16298.
22. McGee DJ, Mobley HL. Pathogenesis of Helicobacterpylori infection. Curr. Opin. Gastroenterol. 2000;16: 24-31.
23. Rizzato C, Torres J, Plummer M, Munoz N, Franceschi S, Camorlinga-Ponce M, et al. Variations in Helicobacter pylori cytotoxin-associated genes and their influence in progression to gastric cancer: implications for prevention. PLoS One 2012;7: e29605.
24. Censini S, Lange C, Xiang Z, Crabtree JE, Ghiara P, Borodovsky M, et al. CagA pathogenicity island of Helicobacter pylori, encodes type I-specific and disease associated virulence factors. Proc. Natl. Acad. Sci. USA, 1996; 93: 14648-14653.
25. Ali H. Al-Marzoqi, HaiderSh. Obaies, Ali M. Saad. Molecular and Cytopathological study on etiological agents responsible of Sexually Transmitted diseases International Journal of PharmTech Research. 2016; 9(6): 357-365.
26. Ali H. Al-Marzoqi, Hawraa J. Kadhim, Ammal R. Shimran, Nebras M. Al-Khafaji, Sabreen A. Kamal, Rusul Adil Naji, Zubaida Amer Faisal, Sarah Abbas Fakhri and Redaah Abd-Alrazzak. Human malignancy associated with Y chromosome: Genotypes and haplotypes associated with susceptibility to Colorectal Cancer patients. Journal of Chemical and Pharmaceutical Research, 2016; 8(4): 919-927.
27. Israa Hussein Noor Hassan, Ali Hussein Al-Marzoqi and Zainab Wahab Maroof. Incidences of glutathione-S transferase genotypes among Iraqi patients associated with chronic myeloid leukemia. International Journal of PharmTech Research. 2016; 9(8):166-173
28. Sheu BS, Yang HB, Yeh YC, Wu JJ. Helicobacter pylori colonization of the human gastric epithelium: a bug's first step is a novel target for us. J Gastroenterol Hepatol 2010; 25: 26-32.
29. Yamaoka Y. Roles of Helicobacter pylori BabA in gastroduodenal pathogenesis. World J Gastroenterol 2008; 14: 4265-4272.
30. Israa Hussein Noor Hassan, Ali Hussein Al-Marzoqi and Zainab Wahab Maroof. Pharmacogenetics and Molecular study on BCR/ABL Inhibitors connected with Chronic Myeloid Leukemia; Genotype variability polymorphism among Babylon population. Journal of Chemical and Pharmaceutical Research, 2016; 8(7): 220-224.
31. Gerhard M, Lehn N, Neumayer N, Borén T, Rad R, Schepp W, Miehlke S, Classen M, Prinz C. Clinical relevance of the Helicobacter pylori gene for blood-group antigen-binding adhesin. Proc Natl Acad Sci USA 1999; 96: 12778-12783.
32. Talebi Bezmin Abadi A, Taghvaei T, Mohabbati Mobarez A, Vaira G, Vaira D. High correlation of babA (2)-positive strains of Helicobacter pylori with the presence of gastric cancer. Intern Emerg Med 2011; Epub ahead of print.
33. Israa Hussein Noor Hassan, Ali Hussein Al-Marzoqi and Zainab Wahab Maroof. Influence of CYP3A5 gene polymorphisms and risk of chronic myeloid leukemia. International Journal of PharmTech Research. 2016; 9(12): 634-639.
34. Oleastro M, et al. Evaluation of the clinical significance of homB, a novel candidate marker of Helicobacter pylori strains associated with peptic ulcer disease. J. Infect. Dis. 2008; 198:1379 –1387.
35. Oleastro M, Monteiro L, Lehours P, Megraud F, Menard A. Identification of markers for Helicobacter pylori strains isolated from children with peptic ulcer disease by suppressive subtractive hybridization. Infect. Immun. 2006; 74:4064–4074.
36. Jung SW, Sugimoto M, Graham DY, Yamaoka Y. homB status of Helicobacter pylori as a novel marker to distinguish gastric cancer from duodenal ulcer. J. Clin. Microbiol. 2009; 47:3241–3245.
37. Tokudome S, et al. Are there any real Helicobacter pylori infectionnegative gastric cancers in Asia? Asian Pac. J. Cancer Prev. 2007; 8:462– 463.
38. SabreenA. Kamal, NisreenKaddim Radi, AliHussein Al-Marzoqi, HawraaSabah Al-Musawiand AfafK. Shuwaikh. Molecular Study for Recurrent Spontaneous Abortions (RSA): the role of HSV, B19, and CMV Markers and Polymorphisms in TLR-3 associated with BOH. International Journal of ChemTech Research. 2017; 10(1):422-428,
39. Westbrook JI, Duggan AE, Duggan JM, et al. A 9 year prospective cohort study of endoscoped patients with upper gastrointestinal symptoms. Eur J Epidemiol, 2005; 20, 619-27.
40. Secka O, Antonio M, Tapgun M, Berg DE, Bottomley C, Thomas V, et al. PCR-based genotyping of Helicobacter pylori of Gambian children and adults directly from biopsy specimens and bacterial cultures. Gut Pathog. 2011; 3: 5-11.
41. Rad R, Gerhard M, Lang R, et al. The Helicobacter pylori blood group antigen-binding adhesin facilitates bacterial colonization and augments a nonspecific immune response. J Immunol 2002;168:3033–41.
42. Ando T, Peek RM, Pride D, et al. Polymorphism of Helicobacter pylori HP0938 reflect geographic origin and correlate with cagA status. J Clin Microbiol 2002;40:239–46.
43. Yamaoka Y. Mechanisms of disease: Helicobacter pylori virulence factors. Nat Rev Gastroenterol Hepatol 2010; 7: 629-641.
44. Talebi Bezmin Abadi A. Therapy of Helicobacter pylori: present medley and future prospective. Biomed Res Int 2014; 2014: 124607.
45. Figura N, Valassina M, Moretti E, Vindigni C, Collodel G, Iacoponi F, Giordano N, Roviello F, Marrelli D. Histological variety of gastric carcinoma and Helicobacter pylori cagA and vacA polymorphism. Eur J Gastroenterol Hepatol 2015; 27: 1017-1021.
46. Yahiro K, Hirayama T, Moss J, Noda M. Helicobacter pylori VacA toxin causes cell death by inducing accumulation of cytoplasmic connexin 43. Cell Death Dis 2015; 6.
47. Yahiro K, Akazawa Y, Nakano M, Suzuki H, Hisatune J, Isomoto H, Sap J, Noda M, Moss J, Hirayama T. Helicobacter pylori VacA induces apoptosis by accumulation of connexin 43 in autophagic vesicles via a Rac1/ERK-dependent pathway. Cell Death Discov 2015; 1: 15035.
48. Feliciano O, Gutierrez O, Valdés L, Fragoso T, Calderin AM, Valdes AE, Llanes R. Prevalence of Helicobacter pylori vacA, cagA, and iceA Genotypes in Cuban Patients with Upper Gastrointestinal Diseases. Biomed Res Int 2015; 2015: 753710.
49. Abadi AT, Mobarez AM, Teymournejad O, Karbalaei M. Concomitant Colonization of Helicobacter pylori in Dental Plaque and Gastric Biopsy. J Pathog 2014; 2014: 871601.
50. Talebi Bezmin Abadi A, Taghvaei T, Mohabbati Mobarez A, Vaira G, Vaira D. High correlation of babA (2)-positive strains of Helicobacter pylori with the presence of gastric cancer. Intern Emerg Med 2011; Epub ahead of print [PMID: 21604199 DOI: 10.1007/s11739-011-0631-6]
51. Tan VP, Wong BC. Helicobacter pylori and gastritis: Untangling a complex relationship 27 years on. J Gastroenterol Hepatol 2011; 26 Suppl 1: 42-45
52. Erzin Y, Koksal V, Altun S, Dobrucali A, Aslan M, Erdamar S, Dirican A, Kocazeybek B. Prevalence of Helicobacter pylori vacA, cagA, cagE, iceA, babA2 genotypes and correlation with clinical outcome in Turkish patients with dyspepsia. Helicobacter 2006; 11: 574-580
53. Zambon CF, Navaglia F, Basso D, Rugge M, Plebani M. Helicobacter pylori babA2, cagA, and s1 vacA genes work synergistically in causing intestinal metaplasia. J Clin Pathol 2003; 56: 287-291.
54. Alm RA, Trust TJ. Analysis of the genetic diversity of Helicobacter pylori: the tale of two genomes. J. Mol. Med. 1999; 77: 834–846.