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Genetic Diversity of *Helicobacter pylori* and its Impact on Disease Outcomes: Host and Environmental Perspectives

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ABSTRACT

Host genetic susceptibility and lifestyle are pivotal factors that determine the incidence and clinical manifestation of persistent infections, including *Helicobacter pylori (H. pylori)*. About 80% of *H. pylori* infected individuals remains asymptomatic throughout their life time, however, the rest of the infected individuals are associated with multiple clinical manifestations including ulcers, gastric cancer and MALT lymphoma. The International Agency for Research on Cancer (IARC), a specialized cancer research agency of the World Health Organization (WHO), has classified *H. pylori* as a class I carcinogen to humans. The onset and severity of diseases associated with Helicobacter pylori are dependent on a structured cascade of bacterial infection and the interplay of multiple host physiological processes and variables. Bacterial virulence factors, including the cag-Pathogenicity Island (cagPAI), VacA, and urease, are critical for the bacterium's ability to colonize and damage the gastric epithelium. Additionally, genetic variability among *H. pylori* strains contributes to differences in disease outcomes and responses to treatment. These factors, in combination, influence the clinical manifestation and progression of *H. pylori*-associated diseases. Considering both host genetic factors and environmental conditions, including diet, hygiene, and antibiotic use, significantly influences the progression and clinical manifestations of *H. pylori* infection. This holistic approach may enable the development of more personalized strategies for combating bacterial infections. This review article explores the multifaceted pathogenicity of *H. pylori* by examining the roles of bacterial virulence factors, genetic variability, and environmental influences.

Keywords: *Helicobacter pylori*, CagA, genetic diversity, environmental factors, microRNAs, bacterial virulence and gastric cancer.

1. INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral-shaped, microaerophilic, Gram-negative bacterium that lives in the human stomach. In 1994, world Health Organization's International Agency for Research on Cancer identified *H. pylori* as a group 1 carcinogen [1]. Colonization of *H. pylori* in the stomach is associated with two major gastrointestinal diseases: peptic ulcer, resulting in approximately 26,700 deaths per year, and gastric cancer, leading to around 782,685 deaths per year [2,3]. While more than 80% of *H. pylori*-infected individuals are clinically asymptomatic, most will exhibit some degree of gastritis. Approximately 10% of infected individuals will develop more severe gastric maladies, such as peptic ulcer disease and atrophic gastritis. Gastric adenocarcinoma and lymphoma of the mucosa-associated lymphoid tissue (MALT) occur in approximately 1% of infected individuals. Approximately 80% of peptic ulcer cases have *H. pylori* infection; others are caused by

non-steroidal anti-inflammatory drugs (NSAIDs). More than 95% of duodenal ulcers and 90% of gastric ulcers are associated with *H. pylori* infection and there is a dramatic decrease in their relapse rate after the *H. pylori* eradication. The impact of *H. pylori* infection on human health is highly variable, leading to ongoing debates about whether it acts as a commensal organism, an opportunistic pathogen, or a true pathogen [4, 5].

Although the virulence factors and role of Helicobacter pylori in peptic ulcers and gastric cancer are well-studied, the varying clinical outcomes and the unclear relationship between H. pylori infection and these diseases remain largely unexplained. Despite infecting approximately 50% of the global population, only 10% to 20% of H. pylori infections result in clinical symptoms such as peptic ulcers or gastric cancer, while the majority of infected individuals remain asymptomatic [6,7]. The mechanisms behind this disparity are not fully understood, but several factors are believed to contribute. These include genetic differences among H. pylori strains, host genetic susceptibility, environmental factors, and differences in immune responses. The bacterium's ability to evade the host's immune system and establish chronic infection without causing immediate disease also plays a role. Furthermore, varying climate and weather conditions have been associated with the development of stomach disorders, particularly concerning peptic ulcer-related bleeding. It has been suggested that environmental factors such as temperature, humidity, and seasonal variations could influence. In warmer climates, bacteria grow more efficiently and can contaminate food [1]. However, many spices used in cooking in warmer regions have antibacterial properties [8]. H. pylori transmission rates, bacterial virulence, and the host's susceptibility to infection. These environmental influences, coupled with the genetic and immunological factors, contribute to the complexity of the relationship between H. pylori infection and the wide spectrum of clinical outcomes observed in different populations. Numerous epidemiological studies have highlighted the link between medications and stomach disorders. Another critical issue affecting clinical outcomes is the development of antibiotic resistance in *H. pylori* due to the promiscuous use of antibiotics and the failure to eradicate the infection completely. Even though the bacterium triggers an immune response through both innate and acquired immunity, the host is unable to eliminate the bacteria from the mucosa, resulting in a lifelong infection. This chronic presence is due to the bacterium's ability to evade immune defenses, manipulate host cell signaling pathways, and induce regulatory T cells that suppress the immune response. Research has investigated genetic polymorphisms in various inflammatory and immunoregulatory cytokines for their potential association with specific H. pylori-associated diseases. Polymorphisms in genes encoding cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α) have been extensively studied. This review explores the impact of genetic polymorphisms in bacterial virulence and host susceptibility genes on disease development, including cancer and immune system functions. It also examines how host genetic susceptibility, the gastrointestinal microbiome, diet, geography, climate, and medications influence clinical manifestations.

2. Bacterial adaptation in gastric milieu

H. pylori is typically transmitted vertically from parents to their infants through oral-oral or fecal-oral routes. It is hypothesized that *H. pylori* began colonizing the human gut approximately 58,000 years ago. Since that time, *H. pylori* and humans have coevolved, with the bacterium adapting to the human gastrointestinal environment and, in turn, influencing human physiology. This long-standing relationship has led to mutual benefits: This evolutionary interplay highlights the complex and reciprocal nature of their relationship over millennia.

Bacterial colonization is a complex, sequential process influenced by multiple factors. It begins with flagellar motility and chemotaxis, which are critical for the colonization and virulence of Helicobacter pylori. Flagellar motility enables H. pylori to navigate through the viscous gastric mucus layer, allowing it to reach and colonize the epithelial surface of the stomach. Chemotaxis, the ability to sense and move toward specific chemical stimuli, directs the bacteria towards more favorable niches within the gastric environment, such as areas with optimal pH levels and nutrient availability. This directed movement is essential for the bacteria to establish a successful infection [9]. *H. pylori*, known as a "good swimmer" due to its lophotrichous flagella (4-8 at one pole) and helicoidal shape, can travel across the viscous gastric mucosa to establish persistent stomach infections. Simultaneously, bacteria secrete extracellular collagenase/pronase proteases, which digest the mucous layer, allowing the organism to pass through it. Upon entering the stomach, *H. pylori* neutralize the acidic environment through the action of a 550kD multimeric nickel-containing enzyme called urease. This enzyme catalyzes the breakdown of urea into carbonic acid and ammonia, thereby neutralizing the local pH around the bacterium [1,10]. The urease enzyme gene cluster comprises structural genes encoding the catalytic subunits (UreA, UreB), an acid-gated urea channel (UreI), and several accessory genes (UreC, UreD, UreE, UreF, UreG, and UreH) [11]. These components work together to maintain a neutral microenvironment, enabling *H. pylori* to survive and thrive in the otherwise hostile acidic conditions of the stomach (Figure 1).

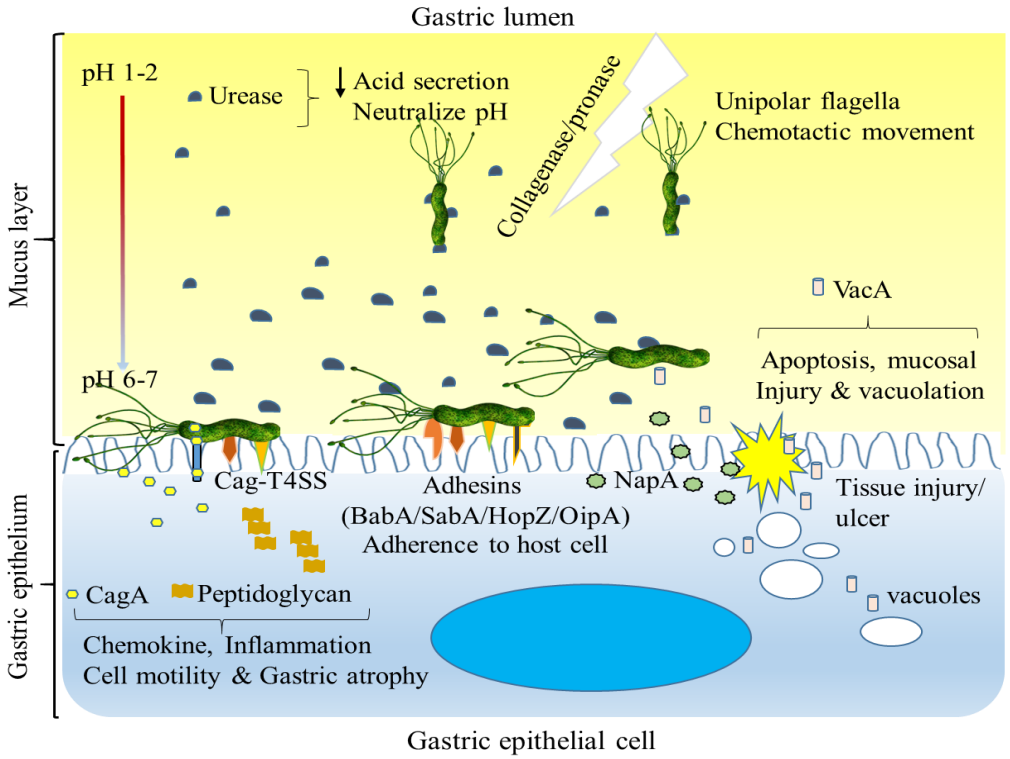

Figure 1. Diagrammatic representation of adaptation of H. pylori in gastric mucosa under stress condition.

H. pylori primarily reside in the gastric antrum region of the stomach and persist there throughout a person's life [12]. It is also capable of colonizing the mucus layer, the inner surface of the epithelium, the inside of the epithelial cells, the fundus, and the entire lining of the stomach. The function of the barrier within the gastric mucosa is crucial in

preventing the toxic substances in the gastric lumen [13]. The gastric mucosal barrier comprises eight components including tight junctions of the epithelial cells, restitution, a process which gastric epithelial cells change shape, secretion of mucosal bicarbonate, the hydrophobic nature of the apical membrane of the gastric epithelial cells, balance of local acid-base and gastric mucous blood flow, production and secretion of gastric mucosa, regulation and protective effect of mucosal prostaglandins and basal lamina [14]. *H. pylori* preferentially attach to the stomach epithelial cells at the apical junctional complex, which comprises tight junctions and adherence junctions. This attachment disrupts the complex that eventually associated with the development of gastric cancer [15,16]. For persistent colonization, *H. pylori* must adhere to the gastric epithelium and avoid being brushed into the intestine. *H. pylori* encode more than 30 outer membrane proteins, many of which are adhesins that help it attach to various sites on host cells. These adhesins interact with the gastric epithelium via fucosylated glycoproteins and sialylated glycolipids as extracellular receptors [17]. For example, BabA and SabA bind to blood group antigen Lewis b and sialyl-Lewis x, respectively. Other protein are AlpA, AlpB, HopH (OipA), HopZ, AhpC, UreA, DupA,CagA, CagI, and CagL, enable the bacterium to adhere to the gastric mucosa under different physiological conditions and deliver toxins to the host cell [17,18]. *H. pylori* exhibits a strong attachment to Lewis b antigens (Leb), an ABO blood group antigen produced on the stomach mucosa, through a mechanism known as blood group antigen-binding adhesion. When *H. pylori* bind to Leb on the epithelial surfaces via BabA, its type 4 secretion system (T4SS) can more effectively exert its pathogenicity [19]. The bacterium has evolved mechanisms to colonize in the stomach environment, while humans have adapted to the presence of *H. pylori*, which may have played roles in modulating the immune system and influencing gut microbiome dynamics.

3. Bacterial virulence, their polymorphism, and clinical outcomes

H. pylori is equipped with several virulence factors that are association with severe form of gastric diseases. The expression of virulence genes varies due to the high genetic diversity among *H. pylori* strains that impact the clinical outcomes in infected individuals. These virulence genes exhibit considerable polymorphism, which affects the prevalence and severity of the diseases. Based on genetic variability, *H. pylori* strains are categorized into two groups: Type I and Type II. Type I strains are more virulent and possess two primary antigens, CagA and VacA, while Type II strains lack these antigens and are considered non-virulent. The roles of these primary virulence factors in the persistence and pathogenesis of *H. pylori* infection are discussed.

3.1. Cytotoxin-associated gene A (CagA):

CagA, an immunogenic antigen encoded by the ~37kbp cag-Pathogenicity Island (cag-PAI), is part of a type IV secretion system (T4SS) that transfers CagA into host cells. CagA interacts with phosphatidylserine (PS) to facilitate its translocation. Inside the host cell, CagA is phosphorylated by Src-family and c-Abl kinases, disrupting host cell signaling pathways [20,21]. Phosphorylated CagA interacts with SHP-2, Grb2, Csk, c-Met, and PLCγ, altering MEK-ERK kinases, inducing cell elongation, membrane polarity, and inflammation. It degrades tumor suppressors RUNX3 and p53, and deregulates the Wnt/β-catenin pathway, leading to gastritis, intestinal metaplasia, and apoptosis resistance [22,23]. Unphosphorylated CagA interacts with ZO1, JAM, E-Cadherin, and PAR1, activating PI3K/Akt, NF-κB, and Wnt/β-catenin pathways, disrupting apical junctions, and inducing mitogenic responses [24]. CagA/SHP2 and CagA/PAR1 interactions alter cell polarity and induce inflammation [25,26]. CagA also impairs dendritic cell function, reducing inflammatory cytokine production and Th1 immune responses [27].

Nearly 70% of all *H. pylori* strains worldwide consist of cagPAI, compared to 95% of East Asian isolates and 60% of Western isolates. The biological activity of CagA is attributed to a well-characterized five-amino acid motif (EPIYA) in the C-terminus region. depending on geographic variation, *H. pylori* strains encode four different forms of EPIYA sequences, EPIYA-A, -B, -C, or -D. Western strains typically consists EPIYA-A, B, and C, whereas East Asian strains have EPIYA-A, B, and D [28, 29]. East Asian strains with EPIYA-D are known to be more virulent than Western Strains with EPIYA-. An increase in EPIYA-C sequences is also associated with increased pathogenicity. A meta-analysis indicated that EPIYA-D raised the risk of stomach cancer in Asian countries by 1.91 times compared to EPIYA-C. Additionally, CagA has multiple repeats of EPIYA-C sequences that associated with more severe form peptic ulcer disease (PUD) and gastric cancer in the USA and Europe [30]. CagA exhibits considerable genetic variation, influencing the bacterium's pathogenicity. *H. pylori* starin carring cagA are associated with morphological and physiological changes in gastric epithelial cells. A recent study found that nucleotide polymorphisms in the cagA gene, such as *cagA1283* and *cagA2551*, are associated with high-grade premalignant lesions. Additionally, polymorphisms such as *cagA2419* and cagA3435, as well as a polymorphism in the *cagL* gene (*cagL400*), were linked to an increased risk of gastric cancer [31]. This shows that genetic differences in these virulence genes play an important role in the transition from infection to severe gastrointestinal disorders. CagA's genetic variability significantly impacts its ability to alter host cell signaling pathways, which leads to increased inflammatory responses and the production of cytokines such as IL-8 and IL-12. This induction of inflammation is crucial in the pathogenesis of gastric diseases [32]. Additionally, specific mutations, such as the K636N variant of *H. pylori*, further enhance its virulence by promoting cancer stem cell-like properties and activating key pathways, including RUNX3, ASPP2, and CDX1 [33]. Studies have shown that individuals harboring more pathogenic CagA variants have a higher risk of developing aggressive gastric diseases, thereby underscoring the clinical significance of this genetic variability [34,35].

3.2. Vacuolating cytotoxin A (VacA): Another key virulence factors is VacA. This protein interacts with many host surface receptor molecules like, growth factor receptor (EGFR) and a glycosylphosphatidylinositol (GPI) and induces various responses, including pore insertion, into the cell membrane, modification of endolysosomal functions, cell vacuolation, apoptosis and, immune inhibition in gastric cultured cell lines [36]. Genetic variation in the VacA gene significantly influences the pathogenic potential of *H. pylori* and its association with various gastric diseases. VacA is categorized into different types, primarily *vacA* s1 and s2, with further subtypes such as *vacA* s1m and *vacA* c1 and d1. The s1 type is generally associated with a higher pathogenicity due to its ability to induce more severe cellular damage, while the s2 type is considered less virulent. Variants such as *vacA* s1m can enhance the toxicity profile by promoting inflammation and cell death [37,38]. The genetic variations in VacA influence several disease outcomes. For instance, strains expressing the *vacA* s1m type are linked to an increased risk of gastric cancer and precancerous lesions, while the *vacA* s2 type is often found in strains that are less associated with severe gastric pathologies [39]. The pore-forming activity of VacA leads to cellular vacuolation and mitochondrial dysfunction, which are critical in the progression of chronic gastritis to more severe conditions, including gastric cancer. Moreover, studies have shown that specific mutations within the vacA gene can further alter its function and impact the host's immune response. These variations can affect the secretion levels of interleukins,

such as IL-8, which is involved in the inflammatory response, thereby influencing disease severity and progression [40].

3.3. Duodenal ulcer-promoting gene (DupA): This protein increases the bacterium's acid tolerance and promotes the synthesis of IL-8 in the stomach mucosa. The *dupA* gene is characterized by two proposed alleles: *dupA1* (intact) and *dupA2* (truncated). Presence of mutation on *dupA* at 1311 and 1426 leads to stop codon called truncated dupA. Research indicates that *dupA1*, unlike *dupA2*, significantly enhances the production of interleukin-12 (IL-12), specifically IL-12p40 and IL-12p70, from CD14+ mononuclear cells [41]. This response is critical for the immune system's ability to combat infections and may influence disease outcomes. Studies involving samples from the United Kingdom, United States, Belgium, South Africa, and China utilized techniques such as PCR, full sequencing, cytokine ELISA, real-time PCR, and flow cytometry to evaluate the functionality of these alleles. The findings emphasize the role of dupA1 in promoting inflammatory responses associated with *H. pylori* infection [42]. The bacterium expresses several phospholipases, including PLA1, PLA2, and PLC, which play a crucial role in its pathogenicity. These enzymes disrupt the gastric mucosal barrier by degrading the phospholipid components, compromising the integrity of the mucosal lining.

3.4. Neutrophil Activating Protein A (NapA): This virulence factor plays a crucial role in the pathogen's ability to cause disease by activating neutrophils, closely associated with the development of dyspepsia. NapA stimulates the production of reactive oxygen species and the release of pro-inflammatory cytokines, contributing to the inflammation and damage seen in *H. pylori*-related gastric disease [43]. *H. pylori* with serine at amino acid 70 (Ser 70-NapA) was more common in dyspeptic patients than *H. pylori* with threonine at the same position (Thr 70-NapA). Mouse neutrophils exposed to Ser 70-NapA showed slightly higher ROS production, suggesting that Ser 70-NapA may delay gastric emptying by inducing ROS and boosting inflammatory cell recruitment [44].

3.5. Serine protease HtrA: This protein also acts as a key bacterial virulence factor that cleaves the cell junction proteins occludin, claudin-8, and E-cadherin, resulting in gastric injury. HtrA was discovered to be present in trimers, and its stability depend on the presence of a leucine or serine residue at position 171. A natural L/S171 polymorphism in *H. pylori* has been discovered that may impact the protease activity of HtrA during infection, which could be clinically significant and influence gastric disease development [45].

3.6. Outer Inflammatory Protein A (OipA). This protein exhibits polymorphisms that significantly influence its role in pathogenicity. OipA enhances the secretion of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-11, IL-17, matrix metalloproteinase 1 (MMP-1), TNF-α, and RANTES, thereby inducing inflammation [46]. This protein also activates the apoptotic cascade, inhibits the maturation of dendritic cells, and plays a role in IL8 induction as well as the delivery of CagA into host cells [47]. Genetic variations in OipA are associated with increased risks of peptic ulcers and gastric cancer [48]. The *oipA* gene expression is regulated by slipped-strand mispairing in a hypermutable CT dinucleotide repeat motif, where changes in CT repeat number cause frame-shift mutations leading to phase variation in *oipA* expression. Recently a study compiled 536 oipA sequences from 10 studies (2000–2019) and examined the relationship between *oipA* phase On/Off status and gastric diseases based on CT repeat number. The data clarified the conservation of the FWLHA peptide-pentamer for phase "On" status, suggesting it as a superior marker over CT repeats. Re-analysis showed a strong association between *oipA* "On" status and gastric cancer

[49]. For example, *H. pylori* isolates from Korea and the United States exhibit significant differences in *oipA* gene characteristics. Korean isolates predominantly have two copies of *oipA* with fewer CT repeats and at least one 'on' phase variant, while US isolates typically have a single *oipA* copy with more CT repeats and a nearly even distribution of 'on' and 'off' phase variants. These geographic variations suggest distinct regional adaptations of *H. pylori* that may influence disease outcomes and host interactions [50].

3.7. IceA gene: It has two alleles, *IceA1* and *IceA2*, which express completely two different proteins. IceA1 is associated with the induction of IL-6 and IL-8 production, contributing to inflammation. Notably, the presence of IceA1 has been linked to more severe clinical outcomes, including an increased risk of peptic ulcer disease [51]. In comparison, iceA2-positive strains are reported to be associated with more prevalent in infected patients.

3.8. Small non-coding RNA of *H. pylori* (HPnc4160): HPnc4160 aids *H. pylori* in adapting to the host and producing oncoproteins. Mutants lacking HPnc4160 colonize mouse stomachs more effectively than wild-type strains. RNA-seq and iTRAQ analyses reveal eight targets of HPnc4160, including genes for outer membrane proteins and CagA. Silencing HPnc4160 leads to increased expression of both OMPs and CagA, suggesting its role in modulating the bacterial pathogenicity and interaction with the host [52].

3.9. Adhesin and outer membrane proteins of *H. pylori*: *H. pylori*'s ability to adhere to the gastric epithelium is crucial for its colonization and persistence, largely facilitated by various adherence genes. Notably, the *babA* gene, which encodes for the blood group antigen-binding adhesin, exhibits significant polymorphism. The BabA protein has variants such as BabA-L, BabA-H, and BabA-ve, which influence its binding affinity to the host's gastric epithelial cells. This variation is associated with differing risks of gastric mucosal damage and gastric cancer, as higher binding affinity typically correlates with more severe disease outcomes. Another critical adherence factor is the CagL protein, part of the type IV secretion system (TFSS). Polymorphisms, particularly at positions Y58 and E59, enhance its binding to the integrin β1 receptor on host cells, leading to an increased risk of gastric cancer [53]. These variations in the CagL gene can significantly influence the severity of *H. pylori*-induced diseases. The Hom family of outer membrane proteins, including HomA, HomB, HomC, and HomD, also plays a role in bacterial adherence. HomB is associated with atrophy and inflammation in the gastric mucosa and is linked to gastric cancer development. The genetic diversity within this family affects the bacterium's ability to adhere and persist, thereby impacting disease progression [54]

Table 1. Genetic variability in virulence genes of *H. pylori* and their contributions to disease.

Gene	Variations/Effects	Function/Role	References
CagA	Western and Eastern variants; K636N enhances cancer properties	Major virulence factor; influences pathogenicity, Gastric Cancer	[29], [33], [35]
VacA	Types s1 (high pathogenicity) and s2 (low pathogenicity); vacA s1m linked to cancer	Induces cellular damage, inflammation, apoptosis and tissue injury.	[38], [39], [55], [56]
dupA	dupA1 (intact) vs. dupA2 (truncated); affects immune response	Enhances IL-12 production	[41], [42]
Nap	Stimulates reactive oxygen species and cytokines	Activates neutrophils and promotes inflammation	[43]

HtrA	HtrA-L171 variant linked to increased cancer risk	Disrupts epithelial barrier, Gastric atrophy	[57]
OipA	oipA gene expression is regulated by slipped-strand mispairing in a hypermutable CT dinucleotide repeat motif, where changes in CT repeat number cause frame-shift mutations leading to phase variation in oipA expression	Enhances secretion of pro-inflammatory cytokines	[46], [47]; [58]
IceA	IceA1 associated with peptic ulcer disease	Induces IL-6 and IL-8 production	[51]
HPnc4160	Silencing increases OMPs and CagA expression	Modulates expression of OMPs and CagA	[52]
BabA	Variants influence binding affinity and disease risk	Adherence factor; binds to gastric epithelium	[59]
CagL	Polymorphisms enhance binding to integrin β1; linked to cancer risk	Part of type IV secretion system, assists CagA transclocation into host cell.	[53]
HomB	Associated with gastric mucosal atrophy and cancer	Contributes to adherence and inflammation	[54]

4. Host defense system against bacterial infection

Both the host genetics, particularly the immune response genes, and the virulence factors of the invading bacteria, decide how severe an infection will become [60]. *H. pylori* has to evade both the innate and adaptive immune responses in order to induce long-term persistent infection. After *H. pylori* invades the gastric mucosa, both adaptive and innate immune responses are triggered to control the infection. NOD1 (nucleotide-binding oligomerization domain 1) and Toll-like receptors (TLRs) are key components of the innate immune system that recognize pathogen-associated molecular patterns (PAMPs). NOD-1 recognizes peptidoglycan of *H. pylori* delivered via type IV secretion system or through outer membrane vesicles, which induces expression of inflammatory cytokines [61,62]. These innate host defense systems activate nuclear factor kappa B (NF-κB), activating protein-1, and interferon regulatory factors through cell signaling pathways. This response is vital for controlling the infection but can also contribute to inflammation and tissue damage if not properly regulated. Due to engagement of NOD-1, the gastric epithelial cells secrete IL-8, main chemoattractant of neutrophils, leads to recruitment of neutrophils to lamina propria which interacts with *H. pylori* factors such as neutrophil-activating protein (HP-NAP) and causes production of cytokines such as IL-12 and IL-23 (Figure 2) [63-65]. It has been reported that NOD-1 gene's rs7789045 TT and rs2709800 TT genotypes are associated with a significant risk of gastric cancer [66]. Gastric epithelial cells produce TLR1, TLR2, TLR4, TLR5, TLR9, and TLR10, which engage with a plethora of *H. pylori* antigens including flagellin, HSP-60, neutrophil-activating protein A, lipoteichoic acid, lipoproteins, lipopolysaccharide, and DNA and RNA [67-69]. The microbial components lipoprotein, lipoteichoic acid, and peptidoglycan are recognized by the TLR-2 [1]. The TLR2-196 to -174 del polymorphism, which modifies the promoter activity and lowers transcriptional activity of the gene, has been linked to a higher risk of stomach cancer in the Brazilian population [70]. Similar to this, the TLR4 gene polymorphisms Asp299Gly (rs4986790) and Thr399Ile (rs4986791) have been demonstrated to be risk factors for gastric cancer in Caucasian and Indian populations [71].

The activation of T helper (Th) cells and specific antibodies is a crucial component of the adaptive immune response, following the initial innate immune response. This coordinated activation ensures a targeted and effective defense against pathogens, facilitating their clearance and contributing

to immunological memory for future encounters [17]. Proinflammatory cytokine encourages CD4+ and CD8+ T cell activation and migration to the stomach environment [72]. Following the polarization of T helper (Th) 1/Th17 responses, a persistent inflammatory response to *H. pylori* infection is developed and this response is then managed by regulatory T (Treg) cells, which are in charge of regulating the inflammatory response [73]. The inflammatory pattern appears to be substantially regulated by age and varies amongst patient groups [74]. Adults often exhibit a preponderance of the Th1 response, coupled with high levels of interferon (IFN-γ), tumor necrosis factor (TNF), IL-1, and IL-8, which are primarily responsible for the attraction of neutrophils and the subsequent establishment of an inflammatory milieu [75-76]. However, earlier research revealed that children's cytokine release patterns and subsequent reactions varied from those of adults.

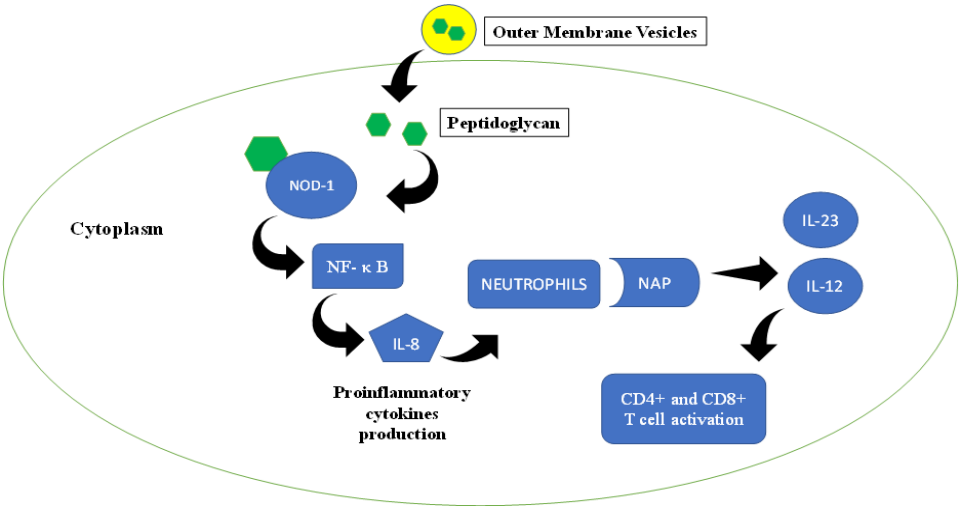

Figure 2. Molecular signaling alterations induced by intracellular delivery of peptidoglycan. *H. pylori* peptidoglycan uses outer membrane vesicles (OMV) to deliver inside the host cell which is recognized by intracellular receptor nucleotide oligomerization domain 1 (NOD1). The recognition involving NOD-1 induces the secretion of IL-8 which leads to recruitment of neutrophils. The neutrophils interact with neutrophil-activating protein (*H. pylori*-NAP) that induces the production of cytokines such as IL-12 and IL-23 which encourages CD4+ and CD8+ T cell activation and migration to the stomach environment.

Children have increased levels of transforming growth factor beta 1 (TGF-β1) and IL-10, cytokines associated with Tregs. In the stomach mucosa, FoxP3+ Treg cell expression was noticeably greater in newborns [77]. Additionally, compared to adults, they showed considerably greater levels of IL-1α and tumor necrosis factor Th1 responses brought on by *H. pylori* have been linked to the onset of corpus gastritis, which can lead to intestinal metaplasia and gastric atrophy, both of which are significant in precancerous lesions.

5. Genetic susceptibility of the host against *H. pylori* infection

The outcome of bacterial infections is largely influenced by the host's genetic susceptibility. Genetic variations in immune response genes can impair a person's ability to recognize and resist infections. Polymorphisms in genes that encode pattern recognition receptors (PRRs), such as TLRs and NOD proteins, can affect immune signaling pathways, resulting in varying inflammatory responses. Furthermore, cytokine gene variants affect the generation and control of immunological mediators, which impact the severity of infections and onset of chronic diseases. Individuals with certain genetic profiles may be more susceptible to infections or have more serious disease outcomes. Understanding these

genetic characteristics is critical for creating effective, personalized approaches to bacterial infection prevention and treatment. Interindividual variation in cytokine response strength is directly influenced by genetic variants, impacting an individual's clinical prognosis (Figure 3) [15]. Polymorphisms in genes like p53, interleukin 10 (IL-10), tumor necrosis factor (TNF), and interleukin 1 (IL-1) affect cytokine expression [78].

H. pylori infection leads to increased expression of activation-induced cytidine deaminase (AID), a protein crucial for somatic hypermutation and class-switch recombination in B cells. This protein normally functions in the immune system but, when overexpressed in gastric cells, causes mutations in the p53 tumor suppressor gene, resulting in controlling cell growth and repair that may contribute to the development of gastric cancer [79]. Likewise, PTPN11 G/A polymorphism at intron 3 (rs2301756) affects the interaction between PTPN11 and *H. pylori* cytotoxin-associated antigens. This interaction activates inflammatory pathways and influences cell apoptosis and proliferation. The G/A polymorphism is associated with reduced gastric atrophy but increased risk of gastric precancerous conditions in individuals infected with *H. pylori* [80-81]. NOD1 is a cytosolic receptor that binds bacterial peptidoglycan and plays a crucial role in the innate immune response. The NOD1 G796A (E266K) mutation in gastric epithelial cells enhances the vulnerability of *H. pylori* infections to lead to intestinal metaplasia and atrophy, making these cells more susceptible to precancerous changes [82]. Similarly, TLR4 acts as a receptor for lipopolysaccharide (LPS), a component of bacterial cell walls, triggering an immune response. TLR4 Polymorphism (+896 A/G, rs4986790) is associated with an increased risk of gastric atrophy (GA). Carriers of the TLR4 +896 G allele have an 11-fold higher risk of developing GA with hypochlorhydria, which is a condition characterized by low stomach acid production [83]. Tahara et al reported the genetic variability in TLR4 at Thr399Ile affects this receptor's function, influencing the immune response to bacterial infections [84]. Other study found that the TLR4 +3725G/C polymorphism (rs11536889) is associated with an increased risk of severe gastric atrophy (GA) in Japanese populations [81]. This finding underscores the importance of genetic variations in host innate immunity, particularly in the context of TLR4 polymorphisms, within East Asian populations. It suggests that individuals with this specific genetic variation might have a heightened susceptibility to severe forms of GA due to altered immune responses to bacterial infections, such as those caused by *H. pylori*.

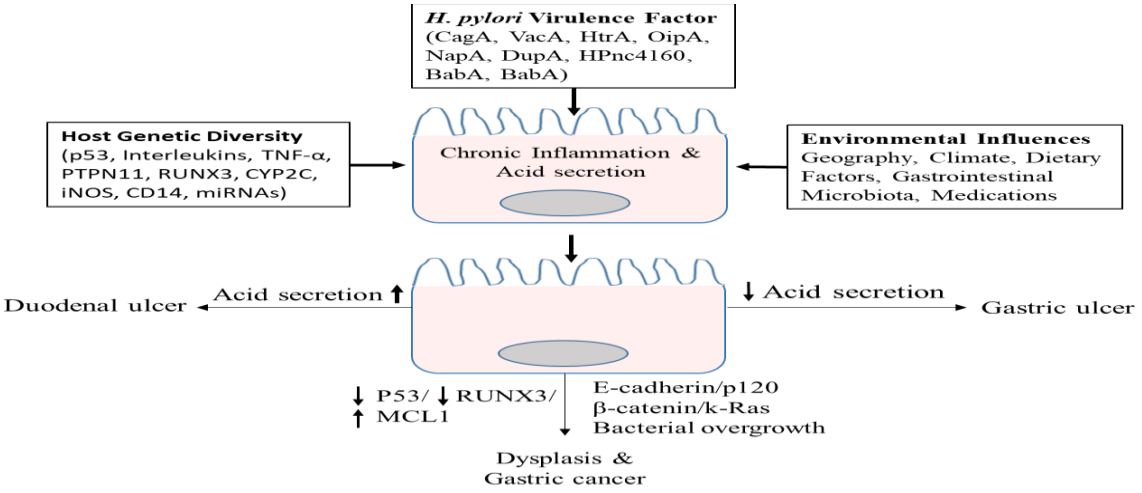

Figure 3. The impact of bacterial virulence factor, Host genetic factors and environmental factors on *H. pylori* pathogenesis.

A study found that the CD14 promoter -159TT variant, as well as individuals carrying the T allele, are associated with a lower risk of gastric atrophy (GA) in *H. pylori*-infected subjects who are 61 years or older [85]. The IL-2 T-330G and IL-2 +114TT polymorphisms are associated with changes in the immune response to *H. pylori* infection. The T-330G variant increases the risk of gastric atrophy and potentially gastric cancer by affecting Th1 responses and reducing gastric acid secretion. The +114TT variant promotes T cell differentiation, influencing the immune system's ability to respond to infection and contributing to inflammation and tissue damage [86]. Interleukin-4 (IL-4) enhances Th2 cell development while inhibiting the Th1 response and impeding the clearance of *H. pylori*. This suppression causes persistent inflammation and mucosal damage, which contributes to stomach atrophy and increases the chance of developing gastric cancer. Genetic polymorphism in IL4 such as IL-4R C-332T (rs1805010), IL-4 −590T and IL-4 −33TT in *H. pylori* infected individuals alter the differentiation of naive helper T cells to Th2 cells that eventually associated with development of gastric atrophy and gastric cancer [87-88].

A study reported that the genetic variation in the iNOS gene including Inducible Nitric Oxide Synthase (iNOS) C150T (rs2297518) and PRKCH rs3783799 G/A is associated with an increased risk of gastric atrophy, particularly in the Japanese population [89]. iNOS is involved in producing nitric oxide, which plays a role in inflammation and immune response. Alterations in iNOS activity can affect gastric mucosal damage and contribute to atrophy. The genetic variation involves a T-to-A substitution at intron 3 of the RUNX3 gene (RUNX3 T/A, rs760805). RUNX3 is a transcription factor that plays a role in regulating various cellular processes, including cell differentiation and tumor suppression. In Japanese individuals, the T/A polymorphism in RUNX3 has been suggested to modulate susceptibility to gastric atrophy. Moreover, research has found associations between eight functional SNPs in the CYP2C family of genes and Peptic Ulcer Disease in 1,239 Caucasian patients. These SNPs include CYP2C8*3 (rs11572080 and rs10509681), CYP2C8*4*, CYP2C9*2*, *CYP2C9*3, CYP2C19*2*, *CYP2C19*3, and CYP2C19*17 [90]. Sun et al reported that the Pepsinogen C (PGC) Ins/Del polymorphism increases the risk of gastric cancer and precancerous conditions. It is also linked to *H. pylori* infection, suggesting that this genetic variation may heighten the risk of gastric cancer when combined with *H. pylori* infection [91]. Similarly, several other genetic polymorphism in cytokines such as IL-1, IL-6, IL8, IL-1β, TNF-α, and IL-10 as listed in the Table 2. Genetic polymorphisms in cytokine genes can significantly influence how the human body responds to *H. pylori* infection and its associated diseases, such as gastric ulcers and gastric cancer. Cytokines are signaling molecules that play a crucial role in the immune response and inflammation. The variations in cytokines can influence the severity of inflammation and susceptibility to gastric diseases, including ulcers and cancer. Understanding these genetic factors can help in predicting disease risk and tailoring treatment strategies.

Table 2. List of the host's genetic polymorphism and their effect on disease outcomes against *H. pylori* Infection.

Host gene polymorphism	Functions/ Effects	Reference
p53 mutation	Increased expression of activation-induced cytidine deaminase (AID) in host cells, causing mutations in the tumor suppressor gene p53.	[79]
PTPN11 G/A polymorphism at intron 3 (rs2301756)	Reduced gastric atrophy and increasing gastric precancerous risk	[24], [81], [89], [92]

Nucleotide- binding oligomerization domain (NOD1) G796A(E266K) mutation	Increased the susceptibility to intestinal metaplasia and atrophy	[82]
TLR4 polymorphism(+896 A/G, rs4986790)	Increased the risk of gastric atrophy with hypochlorhydria.	[83]
TLR4 polymorphism(Thr399Ile, rs4986791))	Acts as a receptor for lipopolysaccharide (LPS) andelicits immune response.	[85]
TLR4 polymorphism (+3725G/C, rs11536889)	Increased the risk of severe gastric atrophy in Japanese and EastAsian populations.	[81]
CD14 C-159T	Lower risk of gastric atrophy	[84]
IL-2 T-330G	Increased risk of gastric atrophy by regulating Th1 immune responsesand inhibiting gastric acid secretion	[86], [93]
IL-2 +114TT	Promotes differentiation of T cells	[86]
IL-4R C-332T(rs1805010) polymorphism	Induce chronic inflammation and risk of developing gastric atrophy	[87]
IL-4 −590T and IL-4 −33TT	Induces differentiation of naive helper T cells to Th2 cells	[88]
Inducible nitricoxide synthase (iNOS) C150T (rs2297518) and PRKCH rs3783799 G/A	Increased the risk of gastric atrophy in Japanese population.	[94]
Runt-related gene 3 (RUNX3) T/A polymorphismat intron 3 (rs760805)	Modulate the riskof gastric atrophy among *H. pylori* seropositive subjects in Japanese people.	[81]
Heat-shock protein 70-2 A/B (A1267G) polymorphism	Impacts the body's inflammatory response and stress handling mechanisms.	[95]
FASL T-844C polymorphism	induce chronic inflammation and affect apoptosis and infiltrating T-cells. Associated with gastric injury and Gastric atrophy	[96]
Pepsinogen C ins/del polymorphism	Increases an individual's susceptibility to gastric cancer and itsprecancerous conditions.	[91]
Eight SNPs in the CYP2C family: CYP2C8*3 (rs11572080 and rs10509681), CYP2C8*4, CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP2C19*3, and CYP2C19*17	Associated with peptic ulcer disease in 1,239 Caucasian patients,	[90], [97]
TLR1- CC andTT genotype ofTLR1 rs4833095	Induce cytokine secretion	[98]
TLR2 -196 to −174 del	Recognizes acylated bacterial lipoproteins and signals	[70]
TLR10- AA genotype ofTLR10 rs10004195	Suppress inflammatory signaling on primary humancells	[98]
NOD-2 R702W (SNP8)	Intracellular recognition molecules for pathogen- associated molecules	[99]
IL-1β -511C/T	Key proinflammatory cytokine in gastric mucosa	[100]
IL-1RN 2/2	Inhibits the activity of IL-1	[101]
IL-6 −174C>G	Regulates the immune system.	[88]
IL-8 −251T>A	Promoter of angiogenesis, act as a chemoattractant	[102]
IL-1β -511C/T	Key proinflammatory cytokine in gastric mucosa	[102]
IL-10 GCC haplotype	Anti-inflammatory cytokine	[103]
TNF-α GA, AA and GA+AA genotypes of TNF-α-308	Key immune mediator against Gram negative bacteria	[104]

6. MicroRNAs in *H. pylori* Infection

MicroRNAs (miRNAs) are small non-coding RNA molecules that play critical roles in regulating gene expression and are increasingly recognized for their involvement in various diseases, including those associated with *H. pylori* infection. Other than host defence impairment, several studies have found the association of expression level of miRNA with progression of infection [105]. For instance, miR-155 is often upregulated in response to infection and is involved in enhancing inflammatory responses by promoting the activation of immune cells [106]. Conversely, miR-146a acts to suppress inflammation and may be downregulated during infection, thus contributing to chronic inflammation and disease progression. MicroRNAs (miRNAs) are ~20-25 nucleotides long, small, non-coding RNAs critical for regulating post transcriptional gene regulation and involved in various important biological processes. The dysregulation in the level of expression of miRNAs have been correlated with acute or chronic inflammation in *H. pylori* infected patients [107]. The aberrant expression of miRNAs classifies the miRNAs as oncogenic (upregulated miRNAs; oncomirs) or tumor suppressors (down-regulated miRNAs) [108, 109]. Here recently published miRNAs in *H. pylori* are listed in the Table 3.

Table 3. A list of H. pylori miRNAs and their role in gastric diseases.

miRNAs	Upregulated/ Downregulated	Biological process affected	Reference
miR-1 and miR-203	Downregulated	gastric cancer development	[110]
miR-21	Upregulated	promote cell survival and proliferation	[111]
miR-29a-3p	Upregulated	Increases migration capacity of gastric epithelial cells; augments EMT induction	[91]
miR-223-3p	Upregulated	Increases migration and proliferation of GC cells	[111]
miR-7	Downregulated	Promotes apoptosis and autophagy; inhibits proliferation and inflammatory response	[112]
miR-153	Downregulated	Promotes apoptosis and autophagy; inhibits proliferation and inflammatory response	[112]
miR-135b-5p	Upregulated	suppress apoptosis and induce cisplatin resistance	[112]
microRNA-204	Downregulated	Enhance BIRC2/TNF-a/NF-kB signaling pathway and promotes angiogenesis and metastasis of gastric cancer cells.	[113]
miR-1298-5p	Downregulated	Inhibits autophagy and promotes gastric cancer development by targeting MAP2K6	[110]
miR-543	Upregulated	Promote cell proliferation, migration, and invasion, induce autophagy inhibition and EMT	[114]
miR-155-5p, miR-150-5p, miR-3163	Upregulated	Alter DNA repair activity and promote genomic instability	[77]
miR-18a-3p and miR-4286	Upregulated	activate inflammation, enhance cancer cell proliferation and motility	[115]
miR-3178	Downregulated	ameliorates inflammation and gastric carcinogenesis by targeting TRAF3	[116]
miR-320a and miR-4496	Downregulated	inhibit CagA tumor activity and metastatic potential	[117]
miR-375	Downregulated	inhibit dendritic cell maturation	[106]
miR-490-3p	Downregulated	Sensitize cancer cells to gefitinib	[118]
miR-203a	Downregulated	Inhibit angiogenesis in gastric mucosa by increasing ANGPT2 expression	[119]
miR-29c	Downregulated	Promotes upregulation of JARID1B and gastric cancer	[120]
Let-7a+	Downregulated	Cell cycle progression, Proliferation, Invasion	[121]
miR-101	Downregulated	Proliferation, Apoptosis, Invasion migration	[122]

Numerous studies have investigated miRNA expression, yet a comprehensive understanding of their roles in various biological processes is still needed. In the context of gastric carcinogenesis, only a limited number of miRNAs have been profiled, despite many showing aberrant expression. However, the specific biological processes affected by these dysregulated miRNAs remain largely unknown. Further research is essential to elucidate their functions and contributions to gastric cancer development.

7. Impact of Environmental Factors on *H. pylori* Infections

In addition to the host genetic makeup and the virulence of the *H. pylori* strain, environmental factors also affect the chance of developing gastric diseases as mentioned in Table 4 [123]. Although the severe gastric disorders are mostly caused by *H. pylori*, "other variables" such as host genetic polymorphisms, GI microbiota, nutrition, medications, geography, and environment have a significant impact on the clinical results. The *H. pylori*-infected persons are more likely to develop specific gastrointestinal disorders, and the severity of these diseases is also influenced by their individual and combined impacts [1]

Table 4. Environmental factors involved in causing *H. pylori* mediated diseases.

Environmental factors	Functions/ Effects	Reference
Geography	Variability in *H. pylori* strains is driven by sanitary conditions, urban vs rural lifestyles, socioeconomic position, and antibiotic use in the community. The geographic variations in the virulence genes are similar to those in the housekeeping genes of *H. pylori*. Compared towealthy nations, *H. pylori* infection is more common in developing nations and environments with limited resources. For example, the prevalence of *H. pylori* infectionin Africa (79.1%), Asia (54.7%), and Latin America and Caribbean region (63.4%) are remarkably higher as compared to the prevalence in North America (37.1%) and Oceania (24.4%).	[1], [7]
Climate	It has been demonstrated that *H. pylori* infection is positively correlated with daily average sunlight time and increases in the expression of Vitamin D receptor in the stomach mucosa. Infection with *H. pylori* is adversely correlated with greater annual average temperatures, and cold areas have considerably higher rates of peptic ulcer disease than hot ones. It was demonstrated through experiments on organotypic mouse stomach slice cultures that cold stress had thecapacity to increase gastrin expression and gastric acid output. The variety in dietary practices in hot and cold climates may also bea factor in the variances in *H. pylori* infectionand the prevalence of gastric disorders that have been documented.	[124][125] [126]
Diet	The chance of contracting atrophic gastritis with intestinal metaplasia and stomach cancerincreases with the consumption of salty food,red meat, processed or smoked meat, and seafood. Vitamin C levels are lower, mucin production is decreased, and ROS levels are higher in the *H. pylori*-infected stomach. Nitrosamines and N-nitroso compounds (NOC), which raise the risk of stomach cancer,are exposed to more exogenously when preserved meat contains preservatives such nitrites. As a result, consuming large amounts of processed meats like bacon, ham, and sausages leads to oxidative stress, which can cause chronic illnesses like stomach cancer. Consuming too much salt can exacerbate NOC.	[127] [128], [129] [130]
Gastrointestinal microbiota	It has been demonstrated in a mouse model that *H. pylori* colonization in the stomach can change the intestinal microbiota. The higher stomach pH or the altered gut immunity may be to blame for the *H. pylori*-infected patients' greater diversity in the intestinal microbiota. It is important to note that most Bifidobacterium-related bacteria are intestinal commensals, and some of them have anti-*H. pylori*, anti-cancer, and anti-ulcer properties.	[1][131] [132]

	Additionally, several Bifidobacterium strains are well-known probiotics that help the host by lowering inflammation. Some of the commensals have also been utilized as probiotics, which employ mechanisms like the production of antioxidants and antimicrobials that can inhibit urease, compete with *H. pylori* for binding to the surface of gastric epithelial cells, block their specific membrane receptors, and stabilize the mucosal barrier of the stomach bypromoting mucus production by surface epithelial cells.	
Medications	An individual may be predisposed to gastrointestinal disorders if they regularly take antacids, antiplatelet medications, SSRIs (selective serotonin reuptake inhibitors), and non-steroidal anti-inflammatory drugs (NSAIDs). A popular NSAID, aspirin, increases plasma levels of pro-inflammatory cytokines like TNF- α, which causes leukocyte infiltration in the stomach mucosa and causes gastrointestinal ulceration. The Proton pump inhibitors' lowering of stomach acid may make it easier for harmful microorganisms to colonize the gut. Long-term usage of these medications raises the risk that it will change the bacteria in the stomach and cause disorders like gastric cancer.	[1] [97] [133]

8. CONCLUSION

The objective of this review was to outline the genetic influences that influence an individual's propensity to develop stomach cancer and peptic ulcers caused by *Helicobacter pylori*. The most prevalent chronic bacterial infection in the world, *H. pylori* also causes serious human disease even though most infected people have no symptoms. While the majority of infections are benign, some *H. pylori* strains cause serious gastrointestinal disorders, showing the involvement of many variables. Variations in the virulence factors of *H. pylori* are the factor that has been investigated the most in this aspect. Even though it has a well-established role inthe development of gastric sickness, *H. pylori* infection alone does not always result in severe gastric disorders. Through this analysis, it has been attempted to elucidate the essential roles played by other predisposing factors, such as host polymorphism and lifestyle choices, in determining clinical outcomes. Since they directly increase an individual's vulnerability to *H. pylori* infection and accompanying disorders, the polymorphisms in host genes encoding immune effector proteins play significant roles in the inter-individual variability in clinical outcomes. Although *H. pylori* is the main culprit behind serious gastric disorders, this review'sdata reveal that "other factors" such as host genetic polymorphisms, GI microbiota, diet, medications, geography, and environment also have a significant impact on clinical outcomes. The severity of certain gastrointestinal disorders that are caused by *H. pylori* infection is also determined by their individual and synergistic effects.

Declaration by Authors

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