CrossMark

Tipping the Scale Towards Gastric Disease: a Host-Pathogen Genomic Mismatch?

Gloria Tavera[1] · Douglas R. Morgan[2,3] · Scott M. Williams[1]

Abstract

Purpose of Review Chronic infection with *Helicobacter pylori* infection is necessary but not sufficient to initiate development of intestinal-type gastric adenocarcinoma. It is not clear what additional factors tip the scale from commensal bacteria towards a pathogen that facilitates development of gastric cancer. Genetic variants in both the pathogen and host have been implicated, but neither alone explains a substantial portion of disease risk.

Recent Findings In this review, we consider studies that address the important role of human and bacterial genetics and ancestry and their interactions in determining gastric disease risk. We observe gaps in the current literature that should guide future work to confirm the hypothesis of the interacting roles of host and bacterial genetics that will be necessary to translate these findings into clinically relevant information.

Summary We summarize genetic risk factors for gastric disease in both *H. pylori* and human hosts. However, genetic variation of one or the other organism in isolation insufficiently explains gastric disease risk. The most promising models of gastric disease risk simultaneously consider the genetic variation of both the *H. pylori* and human host, under a co-evolution model.

Keywords *H. pylori* · Gastric disease · Co-evolution · Disease risk · Genetic ancestry · Genome interaction

Introduction

Gastric cancer is the third leading cause of cancer-related mortality globally and the leading cause of infection-associated cancer mortality, responsible for approximately 723,000 deaths annually or 10% of cancer-related mortality worldwide [1, 2]. It is most prevalent in low-income countries where 5-year survival rates are often less than 15%, as highlighted in the recent CONCORD-3 global cancer survival analysis [3]. *Helicobacter pylori* is the principal cause and the strongest known risk factor for gastric cancer [4]. It was the first bacterium linked to cancer

and is classified by the World Health Organization as a class I carcinogen [5]. However, the inflammation *H. pylori* causes is necessary, but not sufficient, to cause gastric cancer as only a small percentage of infections advance to severe disease [4, 6]. Gastric cancer incidence demonstrates marked geographic variability by region, as demonstrated by the "altitude enigma" in Latin America [7•]. In the USA, it represents a major health disparity, as non-whites have twice the incidence [1].

H. pylori is a gram-negative spiral/rod-shaped bacterium that has evolved to survive a challenging gastric microenvironment. It has adapted to tolerate the low oxygen levels of the stomach, to raise gastric pH with the expression of urease, and to use flagella that allow *H. pylori* to colonize the gastric mucosa [8]. Similar to some other pathogens, including tuberculosis and malaria, *H. pylori* has co-evolved with humans. *H. pylori* is also a commensal bacterium that can be used to trace human migration [9••–15].

H. pylori infection is usually acquired in childhood, and about half of the global population is chronically infected [4]. Some regions in Central and South America have infection rates as high as 90%, [16], but most of these infections result in only mild inflammation ("gastritis") [4]. Some may cause peptic ulcers (10–20%) or gastric adenocarcinoma (1–3%) [17, 18].

This article is part of the Topical Collection on *Genomics*

✉ Scott M. Williams
smw154@case.edu

[1] Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA

[2] Vanderbilt Ingram Cancer Center, Nashville, TN, USA

[3] Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Symptoms of gastric disease do not manifest until the disease has advanced significantly, leading to late diagnoses and high mortality rates [6]. In high incidence/high resource settings such as eastern Asia, screening programs have been shown to decrease gastric cancer mortality, with endoscopy coupled with endoscopic resection for early gastric cancer [19]. *H. pylori* and host genetic factors, acting in concert with dietary, microbiome, and environmental factors, account for progression of a subset of patients along the so-called Correa cascade, from benign non-atrophic gastritis, to multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and lastly adenocarcinoma [17, 20••]. Atrophy, intestinal metaplasia, and dysplasia are considered pre-malignant lesions. The severity of the atrophy and metaplasia is quantified by the OLGA/OLGIM system, and in the research setting by the Correa histopathology score [21].

As the majority of infected individuals do not develop advanced gastric disease, it has been hypothesized that genetic factors of either the host or pathogen mediate disease risk [22]. Studies have supported both genomes as playing a role in disease progression, but thus far they have failed to explain most of the risk. Knowledge of who is at risk of progressing to gastric cancer may help discover biomarkers and design more cost effective interventions, especially in resource-limited settings where the majority of mortality occurs. *H. pylori* eradication in the gastritis stage may prevent gastric cancer [23], but universal population eradication is impractical and potentially harmful for a number of reasons [24]. For example, most infected individuals do not develop disease and therefore, treatment may contribute to antibiotic resistance and disruption of the microbiome. Additionally, as a commensal with effects on the immune system, *H. pylori* may protect from gastro-esophageal reflux disease (GERD), esophageal carcinoma, atopic dermatitis, and childhood asthma [25–29]. Of note, for patients with pre-malignant lesions, *H. pylori* eradication may be helpful as adjunctive intervention, but in general, endoscopic surveillance is needed, particularly in the absence of biomarkers for the risk of progression.

Whether *H. pylori* transitions from commensal bacteria to pathogen strongly depends on host-bacterial genetic interactions [30••]. Accurate and low-cost tools to detect how the two genomes interact and synergize are needed to predict when infection will likely lead to development of gastric cancer. Detailed characterization of study subjects is required for multiple, parallel investigations of host/pathogen genetics, host microbiome, and other molecular determinants that together affect gastric cancer risk.

Altitude and Geography as Determinants of Gastric Disease

Gastric cancer has marked geographic variability at the regional, country, and in-country levels [1]. High incidence regions include eastern Asia, mountainous Latin America along

the Pacific Ocean, and Eastern Europe [2]. Three geographic paradoxes have been observed: the "Altitude enigma", the "African enigma", and the "Asian enigma" [31•]. In Latin America, differences in gastric cancer risk have been observed between human populations living in low versus high altitude regions along the Pacific littoral, the "Altitude enigma" [7•, 30••, 32]. In South and Central America, the incidence of gastric cancer mortality rates in high altitude regions may be as much as 6 times higher than regions at sea level [7•]. It has been suggested that risk factors may cluster in the mountain villages. The "African enigma" refers to the phenomenon of relatively low gastric cancer incidence on most of the African continent, despite almost universal *H. pylori* infection [31•, 33–35]. And the "Asian enigma" notes the high incidence nations in eastern Asia, with a decreasing incidence in the westward transition to India [31•, 36]. These patterns have not been explained by studies of either human or *H. pylori* genetics in isolation.

These "enigmas" are challenged by studies that suggest that factors beyond mere geographical location, such as the genetics of the pathogen or host, are the principal explanatory determinants of gastric cancer risk. However, when analyzed in isolation, these factors have not adequately explained variation in gastric disease outcomes among those infected with *H. pylori*. Since the prevalence of *H. pylori* infection, or even the known *H. pylori* risk gene, *cagA*, in a population generally may not predict gastric disease or gastric cancer incidence [4, 37, 38], this indicates that other factors affect gastric cancer risk within a population. Analyses that incorporate the interaction of both host and pathogen genetics may be better at predicting gastric disease risk than any single factor. Observing gene networks and the impact of the discordance between the genetic ancestries of *H. pylori* and the infected human host has helped determine the likelihood of developing severe gastric disease [30••]. Investigation of these complex interactions may be important for the development of biomarkers and focused prevention programs, as well as gene discovery.

Genetic Determinants of Gastric Disease Risk

In *H. pylori*

H. pylori uses several genes and gene networks to thrive within the gastric microbiome. The *cag* pathogenicity island (PAI) is a series of *H. pylori* genes that encode the type IV secretion system (T4SS), used to transport virulence factors from gram-negative bacteria into host cells that then disrupt key cellular processes of the host [38, 39]. The T4SS is a key enabler of *H. pylori* pathology. The PAI also encodes a secreted *cagA* (*cytotoxin-associated gene A*), oncoprotein-like virulence factor that can cause a severe inflammatory response [40]. Presence of *cagA* associates with increased gastric cancer risk,

and is prevalent in high incidence areas, but is not sufficient to predict who will develop disease [40–42].

The *H. pylori* gene *vacA* also contributes to gastric cancer risk. Located outside of the PAI, this gene encodes a pore-forming cytotoxin that causes vacuole formation in host cells, triggering epithelial cell apoptosis [38, 43]. It also suppresses the host T cell response to *H. pylori* [44]. The *vacAs1 m1* genotype associates with gastric disease [45]. Both *cagA* and *vacA* status and genotype are important carcinogenic risk factors, perhaps independently of host genotype, but they are not definitive determinants of risk for premalignant and malignant gastric lesions [4, 46, 47]. These genotypes alone are insufficient to explain differences in gastric cancer incidence among regions, or to serve as clinical biomarkers.

Other *H. pylori* virulence factors also contribute to a basal inflammatory state necessary for gastric disease progression. These include urease—which creates a microenvironment by neutralizing the low pH of the stomach, periplasmic nitrate reductase—which facilitates iron uptake, and arginase—which aids in *H. pylori* subversion of host macrophages [8, 38, 44]. The maintenance of basal chronic inflammation and subversion of the immune response also partly depends on host genetic factors and responses, mentioned below. Disturbance of the host-pathogen balance results in overt clinical disease. Additionally, the *H. pylori* genome is highly plastic [48], with high recombination rates that enable rapid gain and loss of genetic elements that may be harmful to the host. Although each of the factors in the *H. pylori* genome described above associate with gastric disease, they explain only a very small proportion of attributable risk [49]. Even if they do increase risk, they are not always present, highlighting the plasticity of the *H. pylori* genome and the potential complexity of genomic causes of gastric disease.

Human Factors: Germline and Somatic

Several host genetic factors appear to play a role in influencing gastric disease risk. Both candidate gene and genome wide studies (GWAS) have been used to assess host genetic risk factors. Analyzed independently of the colonizing *H. pylori*, these explain a small proportion of estimated heritability of gastric disease [49]. Based on candidate gene studies, host risk factors for gastric cancer include genes encoding cytokines and cytokine receptors like the interleukin-1 (IL-1) family of cytokines (including IL-1β, IL1RN), IL8, IL-10, TNF-α, stromal remodeling proteins like matrix metalloproteinases, the *MUC1*, *PRKAA1*, and *PTGER4* genes, and prostate stem cell antigen (*PSCA*) that acts as a tumor suppressor gene in gastric pathology [50–55]. In a seminal study by El Omar et al., specific pro-inflammatory cytokine genotypes were associated with gastric cancer risk, in the setting of *H. pylori* infection [56•]. Some *IL-1* SNPs increase inflammation, decrease gastric acid production, and increase gastric cancer risk—in

response to *H. pylori* infection [57]. In the body of gastric cancer risk SNP literature, divergent risk SNPs have been observed in Asian versus non-Asian populations [58•].

GWAS studies have provided further insight into potential germline genetic factors. However, the generalizability of these results is not clear for at least two reasons. First, the majority of gastric cancer GWAS-based analyses have studied East Asian populations. Second, phenotyping in most of these studies has not been as precise as possible. Of the genetic loci listed above, only a few have been corroborated in non-Asian populations. One study, which included non-Asians, only corroborated the role of an *IL1RN2* variant in gastric disease [58•]. A meta-analysis including non-Asians associated zinc finger domain transcription factors and *PSCA* with gastric disease [59]. This evidence was linked to biologically relevant and hypothesis-driven studies. The diverse phenotypes of gastric disease require detailed clinical characterization and sample stratification to yield generalizable results that include disease-associated genes that are both universal and population specific. Only one study has been performed using highly stratified samples [58•], where gastric cancers were stratified by gastric cancer histologic subtype (intestinal or diffuse), anatomic sub-site, *H. pylori* infection status, geographic location (Asian vs. non-Asian), and by a quantitative index of study quality.

As with other infectious diseases, GWAS gastric cancer studies are less informative, compared to those done in noncommunicable diseases [60–62]. Human polymorphisms and polymorphism networks can confer variable effects in the context of different pathogen strains within the same study cohort. Many infectious disease phenotypes depend on complex interactions between host and pathogen genomes. Not surprisingly, most informative infectious disease susceptibility GWAS studies have been done in more genetically homogenous organisms, like *Mycobacterium leprae* [63].

Two GWAS that assessed susceptibility to gastric cancer and *H. pylori* infection identified SNPs with odds ratios up to 1.4, but most were of uncertain biological function and indicate that human genetic variation, considered in isolation, accounts for a small proportion of estimated gastric cancer risk [64–66]. (Table 1) Larger meta-analyses are needed to confirm these associations and assess their importance. Lack of consistency in data collection impacts results and may explain some variability in currently published results.

Human genetics, in concert with epigenetics, may also interact to influence gastric disease risk. A study using ~200,000 SNPs, focused on immune response genes in Colombian populations, reported an association between severity of gastric lesions and exonic SNPs and DNA promoter methylation of the gene *GATA5*. [67] Promoter methylation of *GATA5* and the exonic SNPs in *GATA5* were independently associated with advanced gastric disease and also showed interaction between *GATA5* variants and promoter methylation of the gene,

Table 1 Genetic variants identified by GWAS for phenotypes related to infection by *H. pylori*

Disease/trait	Gene	SNP	Cases/controls	Population	*p* value	OR	95% CI	Reference
Gastric cancer	ZBTB20	rs9841504	1006/2273	Chinese	1.7E-09	0.76	[0.69–0.83]	Shi et al. [64]
Gastric cancer	PRKAA1	rs13361707	1006/2273	Chinese	7.6E-29	1.41	[1.32–1.49]	Shi et al. [64]
H. pylori serologic status	TLR10	rs10004195	2623/7862	European	1.4E-18	0.70	[0.65–0.76]	Mayerle et al. [65]
H. pylori serologic status	FCGR2A	rs368433	2623/7862	European	2.1E-08	0.73	[0.65–0.85]	Mayerle et al. [65]

demonstrating that the association of either factor with gastric disease is modified by the presence of the other. These variants may have complex, pleiotropic effects on the development of gastric disease via modification of tumor suppressors, the inflammatory response, transcript stability, and editing and binding affinity of protein to DNA, as well as cell and tissue differentiation and development of the gastric mucosa. Changes in DNA methylation often occur non-specifically, as a function of aging or environmental factors and some changes may occur in premalignant lesions, making methylation changes potentially useful biomarkers for gastric cancer risk [68–70].

Familial clustering of gastric cancers occurs in 5–10% of cases, and established and emerging germline mutations for the intestinal and diffuse subtypes have been recently summarized [71]. Familial clustering may be partially explained by shared environmental risk factors. Hereditary diffuse gastric cancer (HDGC) was the initially described familial form [72] related to mutations in the E-cadherin gene (*CDH1*). More recent work has implicated germline mutations in *PALB, BRCA1*, and *RAD51C*, in both diffuse and non-diffuse gastric cancer [71]. Additional proof of segregation in families and molecular evidence from tumors is needed to demonstrate an underlying, common genetic basis. Family-specific mutations, if found, could be critical for stratification of gastric cancer risk and treatment as well as further defining important risk pathways.

Comprehensive genetic analyses of gastric cancer tumors, led by the Cancer Genome Atlas Research Network (TCGA), has helped to elucidate various tumor somatic mutations, which yielded a novel classification system based on molecular characterization [73]. TCGA used a series of platforms, including whole-exome sequencing, array-based DNA methylation profiling, mRNA sequencing, microRNA sequencing, reverse-phase protein array, and microsatellite instability testing, to demonstrate that gastric cancers tend to cluster into one of four groups: (1) EBV (9%), with extensive DNA promoter hypermethylation, (2) microsatellite instability (MSI, 21%), with high levels of mutation and hypermethylation of several genes, (3) chromosomal instability (CIN, 50%), with intestinal histology and extensive somatic copy number aberrations, or (4) genomically stable (GS, 20%), with diffuse histology. The TCGA initiative also helps identify specific molecular targets for precision gastric cancer treatment in the future.

Exogenous environmental factors also increase gastric cancer risk, but incompletely explain the distribution of disease risk. These include dietary salt and nitrosamine intake, *H. pylori* virulence factors, presence of non-*Helicobacter* gastric microbiota, medications, alcohol, tobacco, wood smoke exposure in cooking, and availability of micronutrients [74–76]. However, neither exogenous factors, nor host or pathogen genetic variation in isolation has sufficiently explained the distribution of gastric disease. This raises the possibility that context may affect disease risk. For example, the pathogenicity of an *H. pylori* strain varies, depending on genetic variation of the human host and some individuals are better adapted to specific strains than others.

Host genetics may mediate gastric cancer through the microbiome. In a multi-species model, other resident bacteria, as well as viruses and fungi, may act in concert with human and *H. pylori* genetic variants to influence gastric disease risk, but this has not yet been studied across all possible interactions. Some studies have investigated one premise of this hypothesis: whether human genetic variation helps shape overall microbiome composition and if so, how [77]. Human genes associated with metabolism, innate immunity, and vitamin D receptors may modestly influence microbiome composition [77–81]. An especially strong association appears to exist between microbiome composition and C-type lectins [77, 78], which are pattern recognition receptor molecules that recognize microbes and activate inflammation via the immune system. A certain microbiome milieu may create a more inflammatory environment that facilitates gastritis progression. Importantly, advanced atrophy and metaplasia result in hypochlorhydria with a decreased *H. pylori* burden and reconstitution of the non-*H. pylori* microbiota—which may influence further progression to dysplasia and adenocarcinoma [82]. Notably, these individuals, similar to *H. pylori* negative individuals, will have a more diverse gastric microbiome, compared to those who are *H. pylori* positive [82–85]. However, no host genetic determinants have linked microbiome characteristics with gastric disease risk. The role of human genetics in shaping the microbiome, which may in turn impact gastric disease risk, is difficult to explore [86]. Cohorts followed from birth to late adulthood will help clarify the interactions of individual genetics with exogenous factors in shaping the gut microbiome and its potential role in gastric disease.

Co-Evolution as a Determinant of Gastric Disease?

Recent work hypothesized that humans and *H. pylori* reciprocally impact each other's evolution and that gastric cancer risk is higher in host-pathogen pairs that have not co-evolved together [30••]. There is strong evidence that *H. pylori* has co-evolved with geographically defined human populations, moving out of Africa as a host-pathogen complex [87••]. *H. pylori* is usually transmitted vertically from parent to child, enabling host and pathogen genetic factors to be "co-inherited," thus enabling commensalism [88]. Through co-evolution, chronic pathogens with vertical or familial transmission become less virulent over time [89–93], and *H. pylori* infections are well tolerated by humans, causing low-grade inflammation and possibly protecting against allergic and related disorders [25–29, 94, 95]. The *H. pylori* gene *babA2* demonstrates adaptive microevolution with humans [96]. *BabA* binds blood group antigens and triggers pro-inflammatory cytokine release. Amerindians, who almost all carry the O blood group, harbor strains with the *babA* variant that has up to a 1500-fold greater O blood group binding affinity. A human-*H. pylori* pair exhibiting disrupted co-evolution may be partly responsible for triggering more severe gastric disease [97•].

An ideal locale to explore putative *H. pylori*-human co-evolution is Latin America, particularly in the Caribbean basin and surrounding nations. As a result of colonization, Latin America exhibits particularly diverse human and *H. pylori* ancestries [98–100]. A key insight into exploring this concept is based on the observation that Amerindian people living at high altitude suffer disproportionately from gastric cancer, relative to other local populations [30••, 98]. In the mountains, gastric cancer incidence can be up to 25 times that of individuals in low altitude communities [100]. A study of the Colombian coast and mountains demonstrated almost universal *H. pylori* prevalence (~90%), with highly distinct gastric cancer rates [30••]. The low-risk human, coastal population was of mostly African (58%), European, and Amerindian ancestry, while the high-risk (10 × greater), Andean population was mainly of Amerindian ancestry (67%), with some European ancestry. *H. pylori* strains in Colombia also show evidence of substantial admixture, with the historical Amerindian strains being almost universally displaced by European strains [30••, 98]. The high degree of admixture of both humans and *H. pylori* in some areas of Latin America adds to the complexity of the co-evolution model and may further exacerbate gastric disease, and has provided an excellent natural experiment.

When comparing the two Colombian sites, gastric disease severity was less severe in *H. pylori*-human matched samples with similar ancestries [30••]. The proportion of African *H. pylori* ancestry in patients with primarily Amerindian host ancestry correlated with more severe disease. Patients with a primarily African ancestry, infected with African *H. pylori*, had less severe disease. In individuals with high levels of Amerindian ancestry, high percentage *H. pylori* African ancestry was associated with intestinal metaplasia, while a low percentage was associated with gastritis.

The difference in disease prevalence between the mountain and coast populations was accounted for by the interaction effect between African *H. pylori* and Amerindian host ancestry and when modeled with this interaction, the altitude effect disappeared; the interaction effect was approximately five times larger than the effect of *cagA* [30••]. Geographic location, *cagA* and *H. pylori* or human ancestry, considered separately, were poor predictors of risk. The co-evolution model proposes that when *H. pylori* strains co-evolved with humans in Africa for millennia, the result was less severe gastric disease and reduced cancer risk [31•, 33–35, 101]. Since Amerindian people evolved separately from African *H. pylori,* colonization with these "novel" strains in Latin America caused a clash of ancestries, favoring gastric disease and mortality in Amerindian hosts. This suggests that considering ancestry from human samples and their *H. pylori* isolates, together, will identify individuals at greatest risk. It also implies that colonization at two levels has an impact on human disease.

Genome-by-genome interactions that take into account both human host and pathogen genomes should be considered in genetic models of complex, infectious disease, where there is evidence of long-term co-evolution. Examples beyond *H. pylori* include tuberculosis and human papillomavirus [97•]. Hence a bacterium's pathogenicity may depend on human and pathogen genetic factors that are not independent of each other. Such interactions may play an important role in determining the etiology of infectious disease. One genetic variant in either host or pathogen may not be harmful except in the context of the other organism. An individual host may inherit alleles that evolved in a different environment than that of their infecting *H. pylori*; thus, gastric disease may be influenced by a large number of significant human and *H. pylori* genetic interactions, and the effect size of any single two-locus interaction may be small, but this is yet to be determined. Similarity in ancestry between host and *H. pylori* may be an excellent proxy for the paired genetic variation that affects gastric disease risk, while specific loci that confer risk are still being mapped. This creates a new "genetic architecture" to explore, which consists of polygenic susceptibility to infectious disease, influenced by host-pathogen ancestry. Exploring gene-by-gene interactions will be a crucial next step, enabling the discovery of specific genetic loci that are risk determinants, but only in the context of host and pathogen interactions.

H. pylori studies provide some of the best evidence in favor of human-pathogen co-evolution, based on its vertical transmission, long-term colonization of individual hosts, and its approximately 50,000-year association with humans [9••–11, 87••, 95, 101]. *H. pylori*-mediated gastric disease disproportionately occurs in men, while *H. pylori* is usually transmitted

by the mother, which may also indicate the influence of co-evolution, where female fitness may have been more strongly constrained against *H. pylori* virulence [97•, 102, 103]. Although onset of *H. pylori* disease typically occurs during reproductive years, disease usually advances to clinical stages only in late adulthood [97•]. *H. pylori* also recombines often among multiple strains, potentially rapidly acquiring segments that have not co-evolved with local hosts through horizontal gene transfer [104–107]. This could disrupt co-evolution and select for increased virulence, especially in regions where humans and *H. pylori* are highly admixed, such as South America. Therefore, *H. pylori* and human ancestral groups must be considered in the context of each other, in order to predict gastric disease well. As shown with the Latin America altitude effect described above, geographic location is not a significant factor when host-pathogen genetic ancestry is included in the model [30••].

As a highly recombinogenic bacterium, *H. pylori* facilitates the study of co-evolution. Introduction of new microbial competitors and human milieus pressured *H. pylori* to evolve, which may harm the host and in turn influence disease and evolution within the host population. This perpetual host-pathogen evolutionary response, involving different genes and pathways, is likely regionally unique. Humans and pathogens migrating to new environments, or admixing, disrupt co-evolutionary equilibrium and any complementarity developed between host and pathogen. Co-evolutionary interactions tend to promote geographic and spatial variation in disease outcomes, influenced by the local genetic and environmental dynamics that progress towards a unique co-evolutionary equilibrium. Though the role of co-evolution is difficult to definitively prove, all major criteria are met in the case of *H. pylori* and gastric cancer, where patterns of parallel host-pathogen genetic variation have correlated with functional, molecular changes.

Conclusion

A survey of the current literature on the complex etiology and genetic epidemiology of *H. pylori* and gastric disease points strongly to a model where both human and *H. pylori* genetics, including ancestry, influence gastric disease susceptibility, pathogenicity, and progression, depending on each other. Additional studies, in a range of diverse geographic locations, are needed to establish this hypothesis.

If true, understanding local co-evolutionary history and basic tests of individual human and *H. pylori* ancestry may serve as a biomarker to facilitate targeted eradication of *H. pylori* only in individuals at greatest risk, i.e., those with non-co-evolved *H. pylori*. On a macro level, discordance of ancestry between host and pathogen may serve as a proxy for predicting gastric disease. Because local intrinsic and extrinsic

factors influence host-pathogen co-evolution, genetic loci involved in predicting disease may be specific to a geographic region. Studies in different regions will be needed to characterize local co-evolutionary trends. For example, an ancestry-specific co-evolutionary model that applies in Latin America, may not apply in other regions with high gastric cancer incidence, such as eastern Asia. Further elucidation of the co-evolutionary model of disease may contribute a significant paradigm, useful in the study of gastric disease and beyond.

Compliance with Ethical Standards

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.   Ferlay J, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–386.
2.   Torre LA, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
3.   Allemani C, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391: 1023–75.
4.   Wroblewski LE, Peek RM Jr, Wilson KT. *Helicobacter pylori* and gastric cancer: factors that modulate disease risk. Clin Microbiol Rev. 2010;23(4):713–39.
5.   IARC Working Group. IARC monograph on the evaluation of carcinogenic risks to humans: schistosomes, liver flukes and *Helicobacter pylori*. Lyon: International Agency for Research on Cancer; 1994.
6.   Correa P, Piazuelo B. *Helicobacter pylori* infection and gastric adenocarcinoma. US Gastroenterol Hepatol Rev. 2011;7(1):59–64.
7.• Torres J, et al. Gastric cancer incidence and mortality is associated with altitude in the mountainous regions of Pacific Latin America. Cancer Causes Control. 2013;24(2):249–56. **Describes gastric cancer risk in a high-incidence, high-mortality region of Latin America.**
8.   Correa P. The gastric precancerous process. Cancer Surv. 1983;2: 437–50.
9.•• Falush D, et al. Traces of human migrations in *Helicobacter pylori* populations. Science. 2003;299(5612):1582–5. **Reports on methods used to define modern *H. pylori* populations in the**

context of their ancestral gene pools, which are attributable to human migration.

10. Vale F, et al. Dormant phages of Helicobacter pylori reveal distinct populations in Europe. Sci Rep. 2015;5:14333.

11. Dominguez-Bello M, Blaser M. The human microbiota as a marker for migrations of individuals and populations. Annu Rev Anthropol. 2011;40:451–74.

12. Burkitt MD, Duckworth CA, Williams JM, Pritchard DM. *Helicobacter pylori*-induced gastric pathology: insights from in vivo and ex vivo models. Dis Model Mech. 2017;10(2):89–104.

13. Yamaoka Y. Helicobacter pylori typing as a tool for tracking human migration. Clin Microbiol Infect. 2009;9:829–34.

14. Pallen MJ, Wren BW. Bacterial pathogenomics. Nature. 2007;449:835–42. https://doi.org/10.1038/nature06248.

15. Ciesielski TH. Diverse convergent evidence in the genetic analysis of complex disease: coordinating omic, informatic, and experimental evidence to better identify and validate risk factors. BioData Min. 2014;7:10.

16. Castro L, Vaz CL. Helicobacter pylori in South America. Can J Gastroenterol. 1998;12(7):509–12.

17. Correa P. A human model of gastric carcinogenesis. Cancer Res. 1988;48(13):3554–60.

18. Peek RM Jr, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. Nat Rev Cancer. 2002;2(1):28–37.

19. Zhang X, et al. Endoscopic screening in Asian countries is associated with reduced gastric cancer mortality: a meta-analysis and systematic review. Gastroenterology. 2018;155(2):347–54.

20.•• Correa P. Human gastric carcinogenesis: a multistep and multifactorial process–First American Cancer Society award lecture on cancer epidemiology and prevention. Cancer Res. 1992;52(24): 6735–40 **This is the original characterization of how gastric disease progresses.**

21. Mera R, et al. Dynamics of Helicobacter pylori infection as a determinant of progression of gastric precancerous lesions: 16-year follow-up of an eradication trial. Gut. 2017;67(7):1239–46.

22. Chiba T, Seno H, Marusawa H, Wakatsuki Y, Okazaki K. Host factors are important in determining clinical outcomes of Helicobacter pylori infection. J Gastroenterol. 2006;41(1):1–9.

23. Ford A, Forman D, Hunt R, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication for the prevention of gastric neoplasia. Cochrane Database Syst Rev. 2015;7:CD005583.

24. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomized controlled trials. BMJ. 2014;348:g3174.

25. Abnet CC, et al. A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nat Genet. 2010;42:764–7.

26. Wang LD, et al. Genome-wide association study of esophageal squamous cell carcinoma in Chinese subjects identifies susceptibility loci at PLCE1 and C20orf54. Nat Genet. 2010;42(9):759–63.

27. Engel LS, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95(18):1404–13.

28. Vaezi MF, et al. CagA-positive strains of *Helicobacter pylori* may protect against Barrett's esophagus. Am J Gastroenterol. 2000;95(9):2206–11.

29. Blaser MJ, Chen Y, Reibman J. Does *Helicobacter pylori* protect against asthma and allergy? Gut. 2008;57(5):561–7.

30.•• Kodaman N, et al. Human and *Helicobacter pylori* coevolution shapes the risk of gastric disease. Proc Natl Acad Sci U S A. 2014;111:1455–60. **This is the first study to demonstrate that the interaction between host and H. pylori ancestries completely account for severity of gastric lesions.**

31.• Lunet N, Barros H. Helicobacter pylori infection and gastric cancer: facing the enigmas. Int J Cancer. 2003;106(6):953–60. **Demonstrates that H. pylori prevalence does not correlate with**

incidence of gastric disease and that factors beyond mere geographical location must determine gastric cancer risk.

32. Perez-Perez GI, Rothenbacher D, Brenner H. Epidemiology of *Helicobacter pylori* infection. Helicobacter. 2004;9(Suppl 1):1–6.

33. Holcombe C. Helicobacter pylori: the African enigma. Gut. 1992;33(4):429–31.

34. Bravo LE, van Doom LJ, Realpe JL, Correa P. Virulence-associated genotypes of *Helicobacter pylori*: do they explain the African enigma? Am J Gastroenterol. 2002;97(11):2839–42.

35. Campbell DI, et al. The African enigma: Low prevalence of gastric atrophy, high prevalence of chronic inflammation in West African adults and children. Helicobacter. 2001;6(4):263–7.

36. Ghoshal UC, Chaturvedi R, Correa P. The enigma of *Helicobacter pylori* infection and gastric cancer. Indian J Gastroenterol. 2010;29(3):95–100.

37. Román-Román A, et al. Helicobacter pylori vacA s1 m1 genotype but not cagA or babA2 increase the risk of ulcer and gastric cancer in patients from Southern Mexico. Gut Pathog. 2017;9:18.

38. Cover T. Helicobacter pylori diversity and gastric cancer risk. MBio. 2016;7(1):e01869–15.

39. Noto JM, Peek RM Jr. The *Helicobacter pylori* cag pathogenicity Island. Methods Mol Biol. 2012;921:41–50.

40. Tummuru MKR, Cover TL, Blaser MJ. Cloning and expression of a high molecular-mass major antigen of *Helicobacter pylori*: evidence of linkage to cytotoxin production. Infect Immun. 1993;61(5):1799–809.

41. Covacci A, et al. Molecular characterization of the 128-kDa immunodominant antigen of *Helicobacter pylori* associated with cytotoxicity and duodenal ulcer. Proc Natl Acad Sci U S A. 1993;90(12):5791–5.

42. Blaser MJ, et al. Infection with *Helicobacter pylori* strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res. 1995;55:2111–5.

43. Atherton JC, Cao P, Peek RM. Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*. Association of specific vacA types with cytotoxin production and peptic ulceration. J Biol Chem. 1995;270:17771–17,777.

44. Baldari CT, Lanzavecchia A, Telford JL. Immune subversion by *Helicobacter pylori*. Trends Immunol. 2005;26(4):199–207.

45. Atherton JC, et al. Vacuolating Cytotoxin (vacA) alleles of helicobacter pylori comprise two geographically widespread types, m1 and m2, and have evolved through limited recombination. Curr Microbiol. 1999;39(4):211–8.

46. Olbermann P, et al. A global overview of the genetic and functional diversity in the *Helicobacter pylori* cag pathogenicity island. PLoS Genet. 2010;6(8):e1001069.

47. Hatakeyama M. Anthropological and clinical implications for the structural diversity of the *Helicobacter pylori* CagA oncoprotein. Cancer Sci. 2011;102(1):36–43.

48. Suerbaum S, et al. Free recombination within *Helicobacter pylori*. Proc Natl Acad Sci U S A. 1998;95(21):12619–12,624.

49. Lichtenstein P, et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78–85.

50. Schneider BG, et al. Cytokine polymorphisms and gastric cancer risk: an evolving view. Cancer Biol Ther. 2008;7(2):157–62.

51. Tang Y, Zhu J, Chen L, Zhang S, Lin J. Associations of matrix metalloproteinase-9 protein polymorphisms with lymph node metastasis but not invasion of gastric cancer. Clin Cancer Res. 2008;14:2870–7.

52. Song HR, et al. Genetic variations in the PRKAA1 and ZBTB20 genes and gastric cancer susceptibility in a Korean population. Mol Carcinog. 2013;52(Suppl 1):E155–60.

53. Garcia-Gonzalez MA, et al. Association of PSCA rs2294008 gene variants with poor prognosis and increased susceptibility to gastric

cancer and decreased risk of duodenal ulcer disease. Int J Cancer. 2015;137:1362–73.

54. Sakamoto H, et al. Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. Nat Genet. 2008;40: 730–40.

55. Wang Z, et al. Identification of new susceptibility loci for gastric non-cardia adenocarcinoma: pooled results from two Chinese genome-wide association studies. Gut. 2017;66(4):581–587.

56.• El-Omar EM, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature. 2000;404:398–402. **This is a high quality study where pro-inflammatory cytokine genotypes associated with gastric cancer risk, in the setting of _H. pylori_ infection.**

57. El-Omar EM, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology. 2003;124:1193–201.

58.• Persson C, Canedo P, Machado JC, El-Omar EM, Forman D. Polymorphisms in inflammatory response genes and their association with gastric cancer: a HuGE systematic review and meta-analyses. Am J Epidemiol. 2011;173:259–70. **A high quality study that assesses SNPs associated with gastric disease risk in Asian versus non-Asian populations.**

59. Mocellin S, Verdi D, Pooley KA, Nitti D. Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. Gut. 2015;64(8):1209–19.

60. Hill AV. The genomics and genetics of human infectious disease susceptibility. Annu Rev Genomics Hum Genet. 2001;2:373–400. https://doi.org/10.1146/annurev.genom.2.1.373.

61. Jallow M, et al. Genome-wide and fine-resolution association analysis of malaria in West Africa. Nat Genet. 2009;41(6):657–65.

62. Ko DC, Urban TJ. Understanding human variation in infectious disease susceptibility through clinical and cellular GWAS. PLoS Pathog. 2013;9(8):e1003424.

63. Hill AV. Evolution, revolution and heresy in the genetics of infectious disease susceptibility. Philos Trans R Soc Lond Ser B Biol Sci. 2012;367(1590):840–9.

64. Shi Y, et al. A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. Nat Genet. 2011;43:1215–8.

65. Mayerle J, et al. Identification of genetic loci associated with _Helicobacter pylori_ serologic status. JAMA. 2013;309(18): 1912–20.

66. El-Omar EM. _Helicobacter pylori_ susceptibility in the GWAS era. JAMA. 2013;309(18):1939–40.

67. Sobota R, et al. Epigenetic and genetic variation in GATA5 is associated with gastric disease risk. Hum Genet. 2016;135(8): 895–906.

68. Teschendorff AE, et al. Age-dependent DNA methylation of genes that are suppressed in stem cells is a hallmark of cancer. Genome Res. 2010;20:440–6.

69. Schneider BG, et al. DNA methylation predicts progression of human gastric lesions. Cancer Epidemiol Biomark Prev. 2015;24:1607–13.

70. Watanabe Y, et al. Sensitive and specific detection of early gastric cancer with DNA methylation analysis of gastric washes. Gastroenterology. 2009;136:2149–58.

71. Kupfer S. Gaining ground in the genetics of gastric cancer. Gastroenterology. 2017;152:926–46.

72. van der Post RS, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet. 2015;52(6):361–74.

73. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.

74. Haley KP, Gaddy JA. Nutrition and _Helicobacter pylori_: host diet and nutritional immunity influence bacterial virulence and disease outcome. Gastroenterol Res Pract. 2016;2016:3019362.

75. Jakszyn P, et al. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. Carcinogenesis. 2006;27:1497–501.

76. La Torre G, et al. Smoking status and gastric cancer risk: an updated meta-analysis of case-control studies published in the past ten years. Tumori. 2009;95:13–22.

77. Bonder MJ, et al. The effect of host genetics on the gut microbiome. Nat Genet. 2016;48:1407–12.

78. Kurilshikov A, Wijmenga C, Fu J, Zhernakova A. Host genetics and gut microbiome: challenges and perspectives. Trends Immunol. 2017;38(9):633–647.

79. Kolde R, et al. Host genetic variation and its microbiome interactions within the Human Microbiome Project. BMC Gen Med. 2018;10:6.

80. Wang J, et al. Analysis of intestinal microbiota in hybrid house mice reveals evolutionary divergence in a vertebrate hologenome. Nat Commun. 2015;6:6440.

81. Guglielmi G. How gut microbes are joining the fight against cancer. Nature (News Features). 2018;55:482–4.

82. Klymiuk I, et al. The human gastric microbiome is predicated upon infection with helicobacter pylori. Front Microbiol. 2017;8: 2508.

83. Thorell K, et al. In vivo analysis of the viable microbiota and helicobacter pylori transcriptome in gastric infection and early stages of carcinogenesis. Infect Immun. 2017;85(10):e00031–17.

84.• Noto J, Peek R. The gastric microbiome, its interaction with Helicobacter pylori, and its potential role in the progression to stomach cancer. PLoS Pathog. 2017;13(10):e1006573. **This describes some potential drivers of gastric cancer susceptibility, within the complex milieu of the human gastric microbiota.**

85. Dicksved J, et al. Molecular characterization of the stomach microbiota in patients with gastric cancer and in controls. J Med Microbiol. 2009;58:509–16.

86. Rothschild D, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018;55:210–5.

87.•• Linz B, et al. An African origin for the intimate association between humans and Helicobacter pylori. Nature. 2007;445(7130): 915–8. **Study using sequences from large _H. pylori_ dataset describes genetic diversity in _H. pylori_ decreasing with geographic distance from East Africa, from where _H. pylori_ spread around 58,000 years ago, via human migration.**

88. Rothenbacher D, Winkler M, Gonser T, Adler G, Brenner H. Role of infected parents in transmission of _Helicobacter pylori_ to their children. Pediatr Infect Dis J. 2002;21(7):674–9.

89. Anderson RM, May RM. Coevolution of hosts and parasites. Parasitology. 1982;85(Pt 2):411–26.

90. Frank SA. Models of parasite virulence. Q Rev Biol. 1996;71(1): 37–78.

91. Messenger SL, Molineux IJ, Bull JJ. Virulence evolution in a virus obeys a trade-off. Proc Biol Sci. 1999;266(1417):397–404.

92. Schwarz S, et al. Horizontal versus familial transmission of _Helicobacter pylori_. PLoS Pathog. 2008;4(10):e1000180.

93. Agnew P, Koella JC. Virulence, parasite mode of transmission, and host fluctuating asymmetry. Proc Biol Sci. 1997;264(1378): 9–15.

94. Bull JJ, Molineux IJ, Rice WR. Selection of benevolence in a host-parasite system. Evolution. 1991;45(4):875–82.

95. Carroll IM, Khan AA, Ahmed N. Revisiting the pestilence of _Helicobacter pylori_: Insights into geographical genomics and pathogen evolution. Infect Genet Evol. 2004;4(2):81–90.

96. Ansari S, Yamaoka Y. Helicobacter pylori BabA in adaptation for gastric colonization. World J Gastroenterol. 2017;23(23):4158–69.

97.• Kodaman N, Sobota RS, Mera R, Schneider BG, Williams SM. Disrupted human-pathogen co-evolution: a model for disease. Front Genet. 2014;5:290. **Describes a disrupted co-evolution model between host and pathogen, and the need to study genome-by-genome interactions, to explain disease outcome variation, in the context of multiple infectious diseases.**

98. Pazos A, et al. Draft genome sequences of 13 Colombian *Helicobacter pylori* strains isolated from Pacific Coast and Andean residents. Genome Announc. 2017;5(15):e00113–7.

99. Moreno-Estrada A, et al. Reconstructing the population genetic history of the Caribbean. PLoS Genet. 2013;9(11):e1003925.

100. Correa P, et al. Gastric cancer in Colombia. III. Natural history of precursor lesions. J Natl Cancer Inst. 1976;57(5):1027–35.

101. Moodley Y, et al. Age of the association between *Helicobacter pylori* and man. PLoS Pathog. 2012;8(5):e1002693.

102. Thompson JN, Nuismer SL, Gomulkiewicz R. Coevolution and maladaptation. Integr Comp Biol. 2002;42(2):381–7.

103. Cochran GM, Ewald PW, Cochran KD. Infectious causation of disease: an evolutionary perspective. Perspect Biol Med. 2000;43(3):406–48.

104. Ghose C, Perez-Perez GI, van Doorn LJ, Domínguez-Bello MG, Blaser MJ. High frequency of gastric colonization with multiple *Helicobacter pylori* strains in Venezuelan subjects. J Clin Microbiol. 2005;43(6):2635–41.

105. Moodley Y, et al. The peopling of the Pacific from a bacterial perspective. Science. 2009;323(5913):527–30.

106. Wirth T, et al. Distinguishing human ethnic groups by means of sequences from *Helicobacter pylori*: lessons from Ladakh. Proc Natl Acad Sci U S A. 2004;101(14):4746–51.

107. Latifi-Navid S, et al. Ethnic and geographic differentiation of *Helicobacter pylori* within Iran. PLoS ONE. 2010;5(3):e9645.