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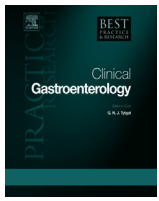

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Clinical relevance of *Helicobacter pylori vacA* and *cagA* genotypes in gastric carcinoma

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Helicobacter pylori infection is the major etiological factor of gastric carcinoma. This disease is the result of a long, multistep, and multifactorial process, which occurs only in a small proportion of patients infected with *H. pylori*. Gastric carcinoma development is influenced by host genetic susceptibility factors, environmental factors, and *H. pylori* virulence. *H. pylori* is genetically highly variable, and variability that affects *H. pylori* virulence factors may be useful to identify strains with different degrees of pathogenicity. This review will focus on VacA and CagA that have polymorphic regions that impact their functional properties. The characterization of *H. pylori vacA* and *cagA*-associated could be useful for identifying patients at highest risk of disease, who could be offered *H. pylori* eradication therapy and who could be included in programs of more intensive surveillance in an attempt to reduce gastric carcinoma incidence.

Introduction

Gastric carcinoma is the fifth most common cancer and the third leading cause of cancer-related death in the world. It is estimated that 952 000 new cases have occurred in 2012. More than 70% of

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the cases occurred in developing countries, where the highest mortality rates for gastric carcinoma are also observed [1].

The great majority of gastric carcinomas are sporadic, with 10% of them having familial clustering, and only 1–3% attributed to hereditary syndromes. There are two main histological variants of gastric carcinoma, the intestinal type, also designated as glandular type, and the diffuse type, also designated as isolated cell type, which exhibit different epidemiological and pathological features [2,3]. Persistent infection with the stomach colonizing bacterium *Helicobacter pylori* is the major trigger for the development of sporadic gastric carcinoma, of both intestinal and diffuse types [4,5]. Gastric carcinoma is the result of a multistep process that begins with the transition from the normal mucosa to chronic superficial gastritis by the action of *H. pylori*. Chronic superficial gastritis can evolve through chronic atrophic gastritis, intestinal metaplasia, and dysplasia to invasive gastric carcinoma [6].

It is estimated that *H. pylori* infects more than half of the world population [7]. Although *H. pylori* infection is associated with a significantly increased risk of gastric carcinoma, not all infected individuals end up developing disease, which suggests a multifactorial aetiology [5]. It is now known that environmental factors such as smoking and high dietary salt intake increase the risk for gastric carcinoma [8–10]. In addition, host genetic factors that influence gastric acid secretion and the inflammatory response to *H. pylori* may play a role in gastric carcinoma development [11–14]. Patients that carry polymorphisms in the genes encoding interleukin-1β, IL-1β receptor antagonist, and tumour necrosis factor-α, that lead to increased IL-1β and TNF-α production, are at higher risk of developing hypochlorhydria, gastric atrophy, and gastric carcinoma in response to *H. pylori* infection [11–14]. Although studies have found conflicting results regarding the relationship between susceptibility polymorphisms and gastric carcinoma risk, this may be explained by variations in laboratory and epidemiologic study quality, differences in ethnicity and in linkage disequilibrium patterns between populations, as well as disease phenotype heterogeneity [15–18].

In addition to environmental and host factors, *H. pylori* strain-specific factors also play a role in gastric carcinoma development [5]. *H. pylori* are genetically highly diverse bacteria, mostly due to high mutational rates, that include large insertions or deletions and chromosomal rearrangements, that affect housekeeping and virulence genes [19]. Genetic variation within *H. pylori* virulence factors may account for differences in the pathogenic properties of strains, and thus may help explain the discrepancies between the number of infected individuals and those that end up developing gastric carcinoma [5]. In this review, and although we are aware that other *H. pylori* virulence factors may contribute to gastric carcinoma pathogenesis, we will mainly focus on CagA and VacA. These are virulence factors that show genetic variation between strains and that have been more extensively studied, thus gaining clinical interest as putative markers of gastric carcinoma [5].

The vacuolating cytotoxin A (VacA)

VacA is a *H. pylori* toxin with multiple cellular effects in different host cell types. The toxin inserts into the cell membrane and forms anion-conducting channels [20]. This property is important for the modulation of other VacA activities such as the ability to induce large acidic vacuoles, which was the first epithelial cell phenotype attributed to the toxin [20–22]. Purified VacA causes gastric epithelial erosions in mice, and *in vitro* induces cell apoptosis by targeting the mitochondria, leading to cytochrome c release and activation of caspase-3 [23–25]. VacA can also cause cell necrosis and interfere with autophagy pathways of gastric cells [26,27]. VacA may additionally have immunomodulatory properties by inhibiting T- and B-lymphocyte proliferation and activation [28,29].

Virtually all *H. pylori* strains produce VacA. However, there is significant variation among strains in their capacity to induce cell vacuolization [30]. This variation is attributed to the genetic structural diversity of the *vacA* gene that can assume different polymorphic rearrangements (Fig. 1(A)) [31,32]. The initial studies on *vacA* detected two main polymorphic regions, the signal (s)- and the middle (m)-regions [32]. The *vacA* s-region encodes the signal peptide and assumes two forms, s1 or s2. The s1 form is active while the s2 encodes a different signal peptide cleavage site which results in a short N-terminal part that displays attenuated vacuolating activity [33,34]. The m-region encodes the VacA