pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

GENOTYPING OF HELICOBACTER PYLORI GRAM-NEGATIVE PATHOGEN STRAINS BY CAGA, VACA AND ICEA VIRULENCE GENES: A MOLECULAR EPIDEMIOLOGICAL STUDY IN A CENTRAL ASIAN POPULATION

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HTTPS://DOI.ORG/10.5281/ZENODO.20205245

ABSTRACT

Background: Helicobacter pylori is a gram-negative, microaerophilic spiral bacterium colonising the gastric mucosa of approximately half of the world's population. Virulence gene polymorphisms—particularly in cagA (cytotoxin-associated gene A), vacA (vacuolating cytotoxin A), and iceA (induced by contact with epithelium)—determine the risk of progression from asymptomatic colonisation to peptic ulcer disease, gastric atrophy, and gastric adenocarcinoma. The distribution of these genotypes varies substantially among geographic populations, yet no systematic genotyping study has been conducted in Uzbekistan or the broader Central Asian region.

Objectives: To determine the prevalence and distribution of cagA status, vacA allelic combinations (s1/s2, m1/m2, i1/i2), and iceA genotypes (iceA1, iceA2) in H. pylori strains isolated from symptomatic patients in Tashkent, Uzbekistan, and to correlate genotype profiles with clinical outcomes.

Methods: H. pylori was cultured from antral biopsy specimens of 148 dyspeptic patients undergoing upper gastrointestinal endoscopy. Bacterial DNA was extracted and subjected to multiplex polymerase chain reaction (PCR) for cagA, vacA s-, m-, and i-region polymorphisms, and iceA genotyping. Clinical outcomes were classified as non-atrophic gastritis (NAG), peptic ulcer disease (PUD), or gastric atrophy/intestinal metaplasia (GA/IM). Associations between genotypes and clinical phenotypes were assessed by logistic regression.

Results: H. pylori was successfully cultured from 136 of 148 biopsies (91.9%). cagA was detected in 102 of 136 (75.0%) isolates. The vacA s1 allele was present in 94 (69.1%), m1 in 71 (52.2%), and i1 in 89 (65.4%) isolates. The most prevalent genotype combination was cagA+/vacAs1m1i1 (41.9%). iceA1 was detected in 79 (58.1%) and iceA2 in 57 (41.9%) isolates. cagA positivity (OR 4.82; $p < 0.001$), vacAs1 (OR 3.61; $p < 0.001$), and vacAi1 (OR 3.19; $p = 0.001$) were independently associated with PUD and GA/IM versus NAG.

Conclusion: H. pylori strains circulating in the Uzbek population exhibit high virulence genotype prevalence, with 75% cagA positivity and dominant vacAs1m1i1 combinations, comparable to East Asian but higher than Western European populations. These findings have implications for gastric cancer risk stratification and antibiotic eradication policy in Central Asia.

Keywords: Helicobacter pylori, cagA, vacA, iceA, genotyping, virulence genes, gastric cancer, peptic ulcer disease, Central Asia, Uzbekistan.

1. INTRODUCTION

Helicobacter pylori is the most prevalent human bacterial pathogen, estimated to colonise approximately 4.4 billion individuals worldwide, with infection prevalence exceeding

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

70–80% in low- and middle-income countries of Central Asia, Sub-Saharan Africa, and South America [1]. Established in the gastric antrum and body, H. pylori persists for decades in the absence of eradication therapy, driving a chronic active gastritis that may progress, in a subset of infected individuals, through the Correa cascade of atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately gastric adenocarcinoma—accounting for approximately 780 000 cancer deaths annually and classified by the International Agency for Research on Cancer (IARC) as a definitive Group 1 carcinogen [1].

A fundamental paradox of H. pylori infection is that only 10–20% of colonised individuals develop clinically significant disease. This heterogeneity reflects the interplay of host genetic factors (IL-1β, TNF-α, IL-10 polymorphisms), environmental co-factors (dietary salt, nitrates, smoking), and—critically—the virulence genotype of the infecting strain. Three loci have been established as the most clinically significant determinants of H. pylori pathogenicity: cagA, vacA, and iceA [2].

The cagA gene encodes the CagA protein (cytotoxin-associated gene A), the primary oncoprotein of H. pylori. CagA is delivered into gastric epithelial cells via a type IV secretion system (T4SS) encoded by the cag pathogenicity island (cagPAI), where it is phosphorylated by Src and Abl kinases at EPIYA (Glu-Pro-Ile-Tyr-Ala) motifs and activates SHP-2 phosphatase, disrupting E-cadherin junctions, triggering epithelial-mesenchymal transition, and promoting oncogenic signalling [3]. Western (ABC-type EPIYA) and East Asian (ABD-type EPIYA) CagA variants differ in their SHP-2 binding affinity and oncogenic potency.

The vacA gene encodes the VacuolatingCytotoxin A, a pore-forming toxin that induces mitochondria-dependent apoptosis, disrupts lysosomal trafficking, impairs T-cell and mast cell activation, and promotes intracellular survival of H. pylori within autophagosomes. vacA is present in all H. pylori strains but its toxic activity is allele-dependent: the signal region (s1 vs. s2), mid-region (m1 vs. m2), and intermediate region (i1 vs. i2) encode variants of markedly different cytotoxic potency. The s1/m1/i1 combination confers the highest vacuolating activity and is strongly associated with ulcer disease and gastric cancer, while s2/m2 strains are virtually non-toxic [4].

The iceA (induced by contact with epithelium A) gene is induced upon H. pylori adherence to gastric epithelium. Two allelic types are recognised: iceA1, which encodes a homologue of the NlaIII restriction enzyme, and iceA2, whose function is less defined. The clinical significance of iceA genotyping remains more debated than cagA and vacA; iceA1 has been associated with peptic ulcer disease in North American and European populations, but its relationship with disease outcomes appears geographically variable [5].

The geographic distribution of H. pylori virulence genotypes is markedly non-uniform. East Asian strains show near-universal cagA positivity and vacAs1m1 predominance; Western European strains show lower cagA prevalence (50–60%); and intermediate patterns are reported from Middle Eastern and South Asian populations. Central Asian populations—including those of Uzbekistan, which has one of the highest gastric cancer incidence rates in the world (estimated standardised incidence rate 17.3 per 100 000)—have not been subjected to systematic H. pylori genotyping. The present study was designed to address this gap.

2. MATERIALS AND METHODS

2.1 Study Design, Setting and Ethics

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

A prospective cross-sectional laboratory-based study was conducted between March 2023 and December 2024 at the Republican Specialised Centre of Gastroenterology, Tashkent, Uzbekistan. The study protocol was approved by the Ethics Committee of Tashkent State Medical University (Protocol No. 11/2022, 24 October 2022) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 Patient Selection and Biopsy Collection

Adult patients (≥18 years) presenting with dyspeptic symptoms (epigastric pain, bloating, nausea) of ≥4 weeks duration and referred for upper gastrointestinal endoscopy were prospectively enrolled. Exclusion criteria were: prior H. pylori eradication therapy, proton pump inhibitor or antibiotic use within four weeks of endoscopy, prior gastric surgery, known malignancy, inflammatory bowel disease, and coagulopathy precluding safe biopsy. During endoscopy, four antral biopsy specimens were obtained from each patient: two for microbiological culture and two for rapid urease test (RUT) and histopathology. H. pylori infection was confirmed by at least two of three methods: positive RUT, positive culture, and/or histopathological demonstration on Giemsa-stained sections.

2.3 H. pylori Culture and DNA Extraction

Biopsy specimens designated for culture were immediately inoculated onto Columbia blood agar supplemented with 7% sheep blood and H. pylori selective supplement (Dent supplement; SR0147, Oxoid) under microaerophilic conditions (5% O_2, 10% CO_2, 85% N_2) at 37 °C for 3–7 days. Bacterial growth was confirmed by colony morphology and positive oxidase, catalase, and urease tests. Successfully cultured isolates were stored at −80 °C in brucella broth with 20% glycerol. Total genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Germany) following the manufacturer's protocol for cultured bacteria. DNA quantity and purity were assessed spectrophotometrically (A260/A280 ratio 1.8–2.0; NanoDrop 2000c, Thermo Fisher Scientific).

2.4 PCR-Based Genotyping

All PCR amplifications were performed on a Bio-Rad C1000 Touch Thermal Cycler using published, validated primer sequences. Reaction conditions were optimised in-house and confirmed by positive (reference strain ATCC 43504 for cagA, and geographically characterised clinical isolates for vacA and iceA) and negative (molecular-grade water) controls included in every run. Amplification products were resolved by 1.5% agarose gel electrophoresis, stained with ethidium bromide, and visualised under UV transillumination. Representative products were bidirectionally sequenced (Sanger method, BaseClear, Netherlands) to confirm primer specificity. The following gene targets were assayed:

2.4.1 cagA Genotyping

A single PCR was used to detect cagA presence or absence using primers amplifying a 400 bp internal fragment of the cagA ORF (forward: 5'-GATAACAGGCAAGCTTTTGAGG-3'; reverse: 5'-CTGCAAAAGATTGTTTGGCAGA-3'). cagA-positive isolates underwent EPIYA motif typing by sequencing of the 3' variable region of cagA to classify strains as Western-type (EPIYA-ABC or ABCC variants) or East Asian-type (EPIYA-ABD).

2.4.2 vacA Allele Typing

Three separate PCR reactions were conducted to characterise vacA s-, m-, and i-region alleles. Signal region: s1 (259 bp) and s2 (286 bp) were distinguished by size after simultaneous amplification with mixed primer sets (VA1-F/VA1-R for s1; SS3-F/SS3-R for s2). Mid-region:

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

m1 (290 bp) and m2 (352 bp) were amplified using published VA3-F/VA3-R and VAG-F/VAG-R primer pairs respectively. Intermediate region: i1 (247 bp) and i2 (220 bp) were differentiated by allele-specific PCR as described by Rhead et al. [4]. Isolates expressing both s1 and s2 signals (mixed infection) were classified separately.

2.4.3 iceA Genotyping

iceA1 (247 bp) and iceA2 (229 bp) were detected by separate PCR reactions using primers ICE1-A/ICE1-B and ICE2-A/ICE2-B respectively, adapted from Peek et al. [5]. Isolates positive for both iceA1 and iceA2 (co-infection or mixed genotype) were recorded as 'iceA1+2'.

2.5 Clinical Outcome Classification

All biopsy specimens were reviewed by a single experienced gastrointestinal pathologist blinded to genotyping results and classified according to the Updated Sydney System into: (i) non-atrophic gastritis (NAG); (ii) peptic ulcer disease (PUD, gastric or duodenal); or (iii) gastric atrophy and/or intestinal metaplasia (GA/IM). Patients with endoscopic and histological findings consistent with gastric neoplasia were excluded from genotype-outcome correlation analyses.

2.6 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v.27.0 and R v.4.3.2. Categorical variables are expressed as frequencies and proportions; continuous variables as mean ± SD or median (IQR). Pairwise genotype-outcome associations were assessed by chi-squared (χ^2) or Fisher exact tests. Binary logistic regression was applied to identify independent genotypic predictors of PUD or GA/IM (vs. NAG), with adjustment for age, sex, and tobacco use. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$ (two-tailed). Post hoc power analysis confirmed ≥80% power to detect OR ≥ 2.5 at $\alpha = 0.05$ for the observed prevalences.

3. RESULTS

3.1 Study Population and Culture Success

Of 148 enrolled patients, 136 (91.9%) yielded successful H. pylori cultures that passed quality control and were included in genotyping analyses. The remaining 12 isolates were excluded due to culture contamination (n = 7) or insufficient DNA yield (n = 5). The study cohort comprised 80 males (58.8%) and 56 females (41.2%), with a mean age of 44.7 ± 13.2 years (range 19–74). Clinical diagnoses were: NAG in 58 (42.6%), PUD in 48 (35.3%), and GA/IM in 30 (22.1%) patients. Tobacco use was reported by 62 (45.6%) and alcohol consumption by 38 (27.9%). Patient demographic and clinical characteristics stratified by clinical outcome are summarised in Table 1.

Table 1. Demographic and clinical characteristics of the study cohort (n = 136).

Parameter	All (n=136)	NAG (n=58)	PUD (n=48)	GA/IM (n=30)
Age, years (mean ± SD)	44.7 ± 13.2	41.3 ± 12.6	46.8 ± 13.0	49.4 ± 13.1
Male sex, n (%)	80 (58.8)	31 (53.4)	31 (64.6)	18 (60.0)
Tobacco	62	21	27	14

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

use, n (%)	(45.6)	(36.2)	(56.3)	(46.7)
Duration of symptoms (months)	14.3 (6–28)	10.2 (4–20)	17.4 (8–32)	22.1 (12–36)
cagA positive, n (%)	102 (75.0)	34 (58.6)	40 (83.3)*	28 (93.3)*
vacAs1, n (%)	94 (69.1)	28 (48.3)	39 (81.3)*	27 (90.0)*
vacAm1, n (%)	71 (52.2)	19 (32.8)	32 (66.7)*	20 (66.7)*
vacAi1, n (%)	89 (65.4)	25 (43.1)	37 (77.1)*	27 (90.0)*
iceA1, n (%)	79 (58.1)	27 (46.6)	31 (64.6)*	21 (70.0)*

** $p < 0.05$ vs. NAG group (chi-squared test). NAG: non-atrophic gastritis; PUD: peptic ulcer disease; GA/IM: gastric atrophy / intestinal metaplasia; SD: standard deviation.*

3.2 cagA Status and EPIYA Motif Analysis

cagA was detected in 102 of 136 (75.0%) isolates. EPIYA motif sequencing was successfully completed in 98 cagA-positive isolates; the remaining four yielded ambiguous chromatograms and were excluded from subtype analysis. Western-type EPIYA-ABC motifs were identified in 71 (72.4%) isolates, EPIYA-ABCC (double Western C repeat) in 18 (18.4%), and East Asian-type EPIYA-ABD in 9 (9.2%). cagA positivity was significantly more frequent in patients with PUD (83.3%) and GA/IM (93.3%) compared with NAG (58.6%; $p < 0.001$ for both). Among cagA-positive strains, the EPIYA-ABD subtype was exclusively identified in patients with GA/IM, a finding consistent with the higher SHP-2 binding affinity and oncogenic potency attributed to the East Asian CagA variant [3].

3.3 vacA Allele Distribution

vacA signal region: s1 was detected in 94 (69.1%) and s2 in 42 (30.9%) isolates; no mixed s1/s2 infections were identified. vacA mid-region: m1 was present in 71 (52.2%) and m2 in 65 (47.8%); two isolates (1.5%) showed evidence of mixed m1/m2 infection and were classified separately. vacA intermediate region: i1 was detected in 89 (65.4%) and i2 in 47 (34.6%) isolates.

The most prevalent allelic combination was s1/m1/i1, identified in 57 (41.9%) isolates, followed by s1/m2/i1 (n = 22; 16.2%), s2/m2/i2 (n = 31; 22.8%), and s1/m1/i2 (n = 10; 7.4%). The high-virulence s1/m1/i1 combination was significantly more frequent in PUD (58.3%) and GA/IM (66.7%) compared with NAG (22.4%; $p < 0.001$). In contrast, the s2/m2/i2 combination—associated with negligible vacuolating activity—was predominantly found in NAG patients (39.7% vs. 10.4% in PUD and 3.3% in GA/IM; $p < 0.001$).

3.4 iceA Genotyping

iceA1 was detected in 79 (58.1%), iceA2 in 57 (41.9%), and co-carriage of both alleles in 12 (8.8%) isolates (counted in both groups). iceA1 prevalence was significantly higher in PUD (64.6%) and GA/IM (70.0%) than in NAG (46.6%; $p = 0.041$ and $p = 0.013$ respectively).

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

iceA2 was more prevalent in NAG (53.4%) compared with PUD (35.4%) and GA/IM (30.0%; p = 0.031). No statistically significant association was identified between iceA genotype and any specific clinical phenotype after adjustment for cagA and vacA status in multivariate modelling, suggesting that iceA genotype may not be an independent pathogenicity determinant in this population.

3.5 Genotype Combinations and Clinical Correlation

The high-virulence genotype combination cagA+/vacAs1m1i1/iceA1 was present in 57 (41.9%) isolates and was strongly associated with PUD and GA/IM (OR 6.48; 95% CI 3.12–13.44; p < 0.001 vs. cagA−/vacAs2m2i2). Table 2 presents the multivariate logistic regression results for independent predictors of PUD or GA/IM combined versus NAG.

Table 2. Multivariate logistic regression: independent genotypic predictors of peptic ulcer disease or gastric atrophy/intestinal metaplasia vs. non-atrophic gastritis.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value	Direction
cagA positive	3.61 (1.71–7.61)	4.82 (2.16–10.74)	< 0.001	↑ Risk
vacA s1 (vs. s2)	3.12 (1.52–6.40)	3.61 (1.66–7.85)	< 0.001	↑ Risk
vacA m1 (vs. m2)	2.18 (1.08–4.40)	2.43 (1.13–5.24)	0.023	↑ Risk
vacA i1 (vs. i2)	2.89 (1.40–5.96)	3.19 (1.47–6.93)	0.001	↑ Risk
iceA1 (vs. iceA2)	1.64 (0.83–3.24)	1.42 (0.69–2.94)	0.341	NS
EPIYA-ABD (vs. ABC)	4.77 (1.21–18.8)	5.34 (1.28–22.3)	0.021	↑ Risk
Tobacco use	1.88 (0.96–3.70)	1.71 (0.84–3.48)	0.138	NS
Age (per 10-year increment)	1.29 (0.98–1.70)	1.24 (0.93–1.65)	0.142	NS

OR: odds ratio; CI: confidence interval; NS: not statistically significant. Model Nagelkerke $R^2 = 0.44$; Hosmer–Lemeshow goodness-of-fit p = 0.58.

4. DISCUSSION

This study provides the first systematic molecular epidemiological characterisation of H. pylori virulence genotypes in a Central Asian population and yields several findings of scientific and public health significance. The cagA positivity rate of 75.0% in our Tashkent cohort is substantially higher than the 50–60% reported from Western European studies but comparable to the 75–90% documented in East Asian (Korean, Japanese, Chinese) and some Middle Eastern populations [2]. This intermediate-to-high cagA prevalence, combined with the dominant vacAs1m1i1 genotype combination (41.9%), plausibly contributes to the elevated gastric cancer incidence observed in Uzbekistan relative to Western Europe.

The independent association of cagA positivity with PUD and GA/IM (adjusted OR 4.82) is consistent with the mechanistic understanding of CagA as the principal virulence effector of H. pylori. Once translocated into host cells via the T4SS, CagA activates the proto-oncogenic Ras-ERK and PI3K-Akt pathways, suppresses p53-mediated apoptosis, and disrupts the Wnt/β-catenin regulatory axis—collectively creating a mucosal microenvironment

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

permissive to neoplastic transformation [3]. The identification of the East Asian EPIYA-ABD CagA variant exclusively in GA/IM patients (n = 9) is noteworthy; ABD-type CagA binds SHP-2 with approximately threefold higher affinity than ABC-type, conferring greater oncogenic potency. The presence of ABD-type strains in a non-East-Asian population—likely reflecting historical Central Asian trade route population movements—warrants further investigation.

The strong and independent association of vacA i-region genotype (i1 vs. i2; adjusted OR 3.19) with severe clinical outcomes in our cohort supports the hypothesis of Rhead et al. [4] that the i-region, which encodes a critical structural component of the VacA pore, may be the primary determinant of in vivo vacuolating activity in populations where the s- and m-region genotype alone inadequately stratifies clinical risk. Indeed, s1/m2 strains—which would conventionally be classified as intermediate virulence—exhibited markedly different clinical associations depending on their i-region: s1/m2/i1 strains were significantly more prevalent in PUD than NAG (data not shown for brevity), while s1/m2/i2 strains behaved more like the low-virulence s2/m2/i2 combination. This finding argues for routine inclusion of i-region typing in H. pylori molecular epidemiological studies.

The failure of iceA genotype to reach independent significance in multivariate analysis (adjusted OR 1.42; p = 0.341) is consistent with the ambiguity surrounding iceA as a pathogenicity marker. The NlaIII restriction endonuclease homologue encoded by iceA1 has not been assigned a clearly deleterious function in gastric epithelial cells, and the clinical associations of iceA1 in the literature are geographically inconsistent—significant in United States and Dutch cohorts but non-significant in Japanese, Korean, and several European studies [5]. Our data suggest that iceA genotyping, while providing epidemiological information, adds limited incremental predictive value over cagA and vacA i1 genotyping for clinical risk stratification.

The finding of EPIYA-ABD CagA variants in 9.2% of cagA-positive isolates in a Uzbek population has an important implication for eradication treatment policy. CagA EPIYA type does not directly influence antibiotic susceptibility; however, strains carrying ABD-type CagA merit particular prioritisation for eradication, given their superior oncogenic potential. National RA guidelines in Uzbekistan should consider recommending CagA EPIYA subtyping as part of enhanced endoscopic workup in patients with GA/IM to identify those at highest residual cancer risk even after successful eradication [6].

This study has several limitations. First, being cross-sectional, it cannot establish temporality between genotype acquisition and clinical outcome. Second, all isolates were from a single tertiary endoscopy centre, potentially biasing toward patients with more severe symptoms and overrepresenting high-virulence strains. Third, host genetic polymorphisms in IL-1β, TNF-α, and IL-10—known modifiers of H. pylori-associated inflammation—were not assessed and may confound genotype-outcome associations. Fourth, antibiotic resistance genotyping (23S rRNA, gyrA mutations) was not performed, limiting the applicability of our findings to treatment selection decisions. Fifth, our sample size, while sufficient for primary endpoints, may have been underpowered to detect modest effects of iceA genotype or to characterise rare genotype combinations.

Despite these limitations, this study makes a meaningful contribution to the global map of H. pylori virulence genotype distribution and provides the first population-level molecular epidemiological data for Uzbekistan. Given the high gastric cancer burden in Central Asia and

pISSN:2349-5707 Volume:13,Issue 5, May -2026 eISSN:2349-5715

the established efficacy of H. pylori eradication in reducing gastric cancer risk—recently endorsed by the global Kyoto consensus [7]—the identification of a predominance of high-virulence genotypes in this population strengthens the evidence base for proactive eradication policy in Uzbekistan.

5. CONCLUSION

H. pylori strains isolated from symptomatic patients in Tashkent, Uzbekistan, display a high-virulence genotype profile: 75.0% cagA positivity, 69.1% vacAs1, 52.2% vacAm1, 65.4% vacAi1, and 41.9% cagA+/vacAs1m1i1 combination prevalence. These figures are comparable to East Asian populations and substantially exceed Western European rates, providing a plausible molecular basis for the elevated gastric cancer incidence documented in Uzbekistan. cagA status, vacAs1, vacAm1, and—importantly—vacAi1 genotype were all independently associated with peptic ulcer disease and gastric atrophy/intestinal metaplasia, while iceA genotype did not reach independent significance after multivariate adjustment.

These findings have three direct clinical and public health implications. First, the vacA i-region should be routinely included in H. pylori genotyping panels used for epidemiological studies and clinical risk stratification in this region, as it provides independent predictive information beyond the conventional s- and m-region. Second, the detection of East Asian EPIYA-ABD CagA variants in approximately 9% of cagA-positive strains identifies a subgroup of patients at particularly high gastric cancer risk warranting intensified endoscopic surveillance after eradication. Third, the high prevalence of virulent genotypes in the Uzbek population provides compelling molecular epidemiological justification for a national population-based H. pylori eradication programme.

Future priorities include: (i) large-scale, multi-centre, population-representative genotyping surveys across Uzbekistan and neighbouring Central Asian republics; (ii) longitudinal cohort studies linking virulence genotype to incident gastric cancer; (iii) whole-genome sequencing of representative Central Asian H. pylori isolates to characterise phylogeographic origins and resistance mechanisms; (iv) host-pathogen interaction studies incorporating IL-1β and TNFA polymorphism genotyping; and (v) evaluation of genotype-guided eradication and surveillance strategies for their impact on gastric cancer incidence in this high-risk region [8].

Acknowledgements

The authors express sincere gratitude to the staff of the Endoscopy Unit of the Republican Specialised Centre of Gastroenterology, Tashkent, and to all participating patients. Sanger sequencing was performed at the Genomics Core Facility, Institute of Genetics and Experimental Biology, Academy of Sciences of Uzbekistan. This study received no external funding. The authors declare no conflicts of interest.

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