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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Martínez-Martínez FJ, Chiner-Oms Á, Furió V, et al. Genomic determinants of antibiotic resistance for *Helicobacter pylori* treatment: a retrospective phenotypic and genotypic observational study. *Lancet Microbe* 2026. https://doi.org/10.1016/j.lanmic.2025.101217

Supplementary File

Title: Genomic determinants of antibiotic resistance for *Helicobacter pylori* treatment: a retrospective, phenotypic and genotypic observational study

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Extended methods

A full description of sampling, bacterial isolation, DNA extraction, long-read sequencing and assembly can be found in the first article of the *Helicobacter pylor*i Genome Project (*Hp*GP) published by Thorell and Muñoz-Ramírez *et al*.[1]

Sample acquisition

*Hp*GP samples were collected from a variety of sources and contributors were identified in international scientific meetings, direct invitations, and referrals. Spain was oversampled due to its colonial impact in Latin America. Sample collection included gastric tissues and cultures from patients with various gastric conditions collected between 1995 and 2020. Eligibility of the biospecimens was confirmed by the US National Cancer Institute and then sent to Vanderbilt University to be processed. A total of 1,011 *H. pylori* strains were analyzed.

Distribution of sample collection and resistance prevalence over time

Our dataset was composed of samples collected in the last 30 years. To perform this analysis, we focused on the phenotyped *Hp*GP samples, collected specifically between 1995 and 2020. In the case of the samples for which we do not dispose of the exact year of collection but a year interval, we consider the mean year. We grouped the samples by 5 years and calculated the resistance prevalence, i.e. the number of samples resistant during that period divided by the total amount of samples from that period.

Minimum Inhibitory Concentration (MIC) test for clarithromycin and levofloxacin resistance

Agar or broth dilution methods are considered the reference methods for MIC calculation. However, these have rarely been used with *H. pylori* since this pathogen barely grows in broth.[2] In this study, Etest method has been chosen since it is a quantitative method with a direct expression of MICs and is adapted to slow-growing bacteria like *H. pylori*. In addition, available literature shows a good correlation between this method and agar dilution method.[3] A quality control in order to verify the compliance of the media used for antibiograms and Etest strips (bioMérieux) to determine MICs was conducted using the *H. pylori* strain CCUG 17874, from the Culture Collection University of Gothenburg (Gothenburg, Sweden).

Isolation and DNA extraction

Gastric tissues were homogenized and plated on selective agar for bacterial growth. *H. pylori* colonies were then identified using Gram staining and biochemical assays. For each sample, a pool and one single colony were expanded and frozen. In addition, the single colony was also expanded, and its DNA was extracted using Qiagen kits. The original cultures were processed likewise.

Whole-Genome sequencing with Pacbio

DNA sequencing was performed at the US National Cancer Institute using PacBio RSII, Sequel and Sequel II instruments. The libraries were prepared using the SMRTbell Template Prep Kit as recommended by the manufacturer.

Genome assembly

Data obtained from the different PacBio instruments were standardized and analyzed using SMRTLink's HGAP4/Microbial Assembly and Hifiasm v0.13-r308. Contigs were circularized and validated for accuracy and the chromosomal sequences were compared with a reference *H. pylori* strain to confirm high homology.

Pubmed search to find mutations described with clarithromycin and levofloxacin resistance

At the beginning of the study, we used the following Pubmed search query to identify the mutations of interest, if any: ("Helicobacter pylori"[MeSH Terms] OR "Helicobacter pylori"[All Fields]) AND ("drug resistance"[MeSH Terms] OR "resistance"[All Fields]) AND ("clarithromycin"[All Fields] OR "levofloxacin"[All Fields]) AND ("mutation"[All Fields] OR "genetic determinants"[All Fields] OR "genomics"[All Fields]). The search was performed on January 10, 2022, and restricted to all scientific articles published until then. No language or article type restrictions were included

Statistical association of mutations and phenotypes using a targeted approach

The *23S rRNA* and *gyrA* and *gyrB* sequences from the 1,011 *Hp*GP genomes were extracted with BLASTN v2.5.0, using the *H. pylori* reference genes (GenBank accessions: U27270.1:372-3339 for *23S rRNA*, CP079087.1:752290-754773 for *gyrA* and CP079087.1:527460-529781 for *gyrB*). For each gene, a multiple sequence alignment using MAFFT v7.407 was performed,[2] specifying the parameter '–keeplength' to maintain the genomic coordinates of the reference sequence for the variant identification and posterior analysis. Later, snp-sites v2.5.1 were run specifying the parameter -v to obtain a VCF file from our alignment.[3] Then, taking only the variants of the 419 phenotyped strains as input, we designed a custom R code that counts, for each variant, the number of wildtype and mutant resistant and susceptible strains in the dataset. With this information, a one-tailed upper Fisher's exact test was performed as we were interested in finding those mutations positively associated with resistance. The resulting p-values were corrected with a Bonferroni test to identify potential variants directly involved in antimicrobial resistance by multiplying the p-values by the number of comparisons, i.e., 366 in the case of *23S rRNA* gene,1154 in the case of *gyrA* gene and 1235 in the case of *gyrB* gene. R version 4.3.2 with

the packages stringr v1.5.1, ggplot2 v3.5.1, and the native package stats v.4.3.2 were used in this part.

Association between genotype, *H. pylori* subpopulation, and MIC levels

A Chi-square test was performed to assess the presence of an association between the assigned *H. pylori* subpopulation according to Thorell and Muñoz-Ramírez *et al.*,[1] and the genotype for each strain, focusing on *23S rRNA* and *gyrA* genes. Similarly, a Mann-Whitney U-test was conducted to investigate whether differences in MIC values are linked to specific mutations in those genes (normality of the distribution was not confirmed using the Shapiro-Wilk test, alpha < 0·05 in all categories). R version 4.3.2 with the ggplot2 v3.5.1 and dplyr v1.1.4 packages and the native package stats v4.3.2 were used in this part.

Global, genomic-based prevalence of clarithromycin and levofloxacin resistance

We used FASTP v0.12.5 to remove low-quality reads,[4] mapped the reads with BWA v0.7.17-r1188 against the *23S rRNA* (GenBank: U27270.1:372-3339) and *gyrA* (GenBank: CP079087.1:752290-754773) references to keep only those genes for further analysis,[5] prepared a mpileup file with SAMTOOLS v1.19.2 and used it to call the SNPs using VarScan v2.3.7,[6,7] obtaining the final VCF file. Strains carrying the resistance-associated mutations for the *23S rRNA* and *gyrA* genes were identified.

Screening of resistance-conferring mutations for other antibiotics in the *Hp*GP dataset

The regimens for which we estimated prevalence of resistance strains contain a diverse set of drugs. All triple clarithromycin-, metronidazole- and rifampicin-based therapies contain a proton pump inhibitor (PPI), clarithromycin, metronidazole and rifampicin accordingly, and amoxicillin. Sequential therapy includes a PPI and amoxicillin in the first phase, and a PPI, clarithromycin and metronidazole in the second phase. Concomitant therapy includes a PPI, amoxicillin, clarithromycin and metronidazole. Hybrid therapy contains a PPI, amoxicillin, clarithromycin and metronidazole. Reverse hybrid therapy contains a PPI, amoxicillin, clarithromycin and metronidazole. Novel concomitant therapy includes a PPI, amoxicillin, clarithromycin and metronidazole. Bismuth-based therapy can contain metronidazole or levofloxacin, plus a PPI, a bismuth salt, amoxicillin or tetracycline. Finally, levofloxacin-containing therapy includes a PPI, levofloxacin and amoxicillin.

Extended results

Distribution of sample collection and resistance prevalence over time

We explored the trends of prevalence for clarithromycin and levofloxacin according to the collection date of the 419 phenotyped *Hp*GP samples collected between 1995 and 2020. As shown in Supplementary Figure 1, samples were mostly collected between 2015 and 2020, with lower sampling in the previous years. Resistance prevalence for clarithromycin and levofloxacin show a slight positive trend, but since the number of samples strongly increases through time, conclusions may be misleading. However, as shown in Appendix 2 p 20, our prevalence estimations overall agree with published data, and as such, we expect this trend to match existing studies.

Association of genotypes and ancestral subpopulations

A Chi-square test showed a positive association for the subpopulations hspSWEurope (p-value = 0·0031), hspEAsia (p-value = 0·0057), and hspEurasia (p-value = 0·001), and an inverse association for hspSWEuropeLatinAmerica (p-value = 0·00035) and hspNEurope (p-value = 0·018) (Supplementary Figure 2A) with the *23S rRNA* mutated genotypes, meaning that, respectively, these subpopulations showed a higher and lower frequency of *23S rRNA* mutations than would be expected by chance. Apart from hspEAsia, hspEurasia and hspSWEurope, for which the number of strains is above 40, the number of strains that belong to the other groups was small to perform an individual analysis. Therefore, these populations were pooled in Supplementary Figure 2B to show a broader view of the mutations' frequencies.

For the *gyrA* genotypes (Supplementary Figure 2C), mutations on both 87 and 91 codons were found in almost all the population groups, except for hspIndigenousAmerica (only N87K) and hspAfrica1WAfrica (only N87I). However, in these two groups there was only one phenotyped strain for levofloxacin. Smaller populations were pooled in Supplementary Figure 2D to provide a broader view of the frequencies.

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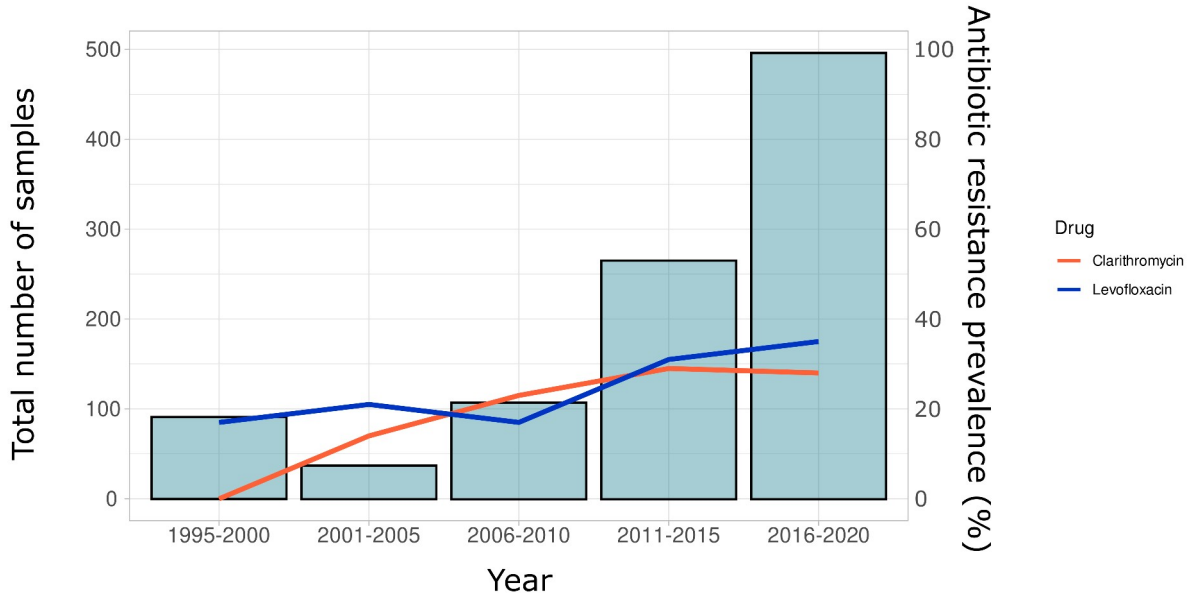
Supplementary figures



Supplementary Figure 1. Trends of clarithromycin and levofloxacin resistance prevalence over a 25 years period according to the 419 phenotyped *Hp*GP samples.

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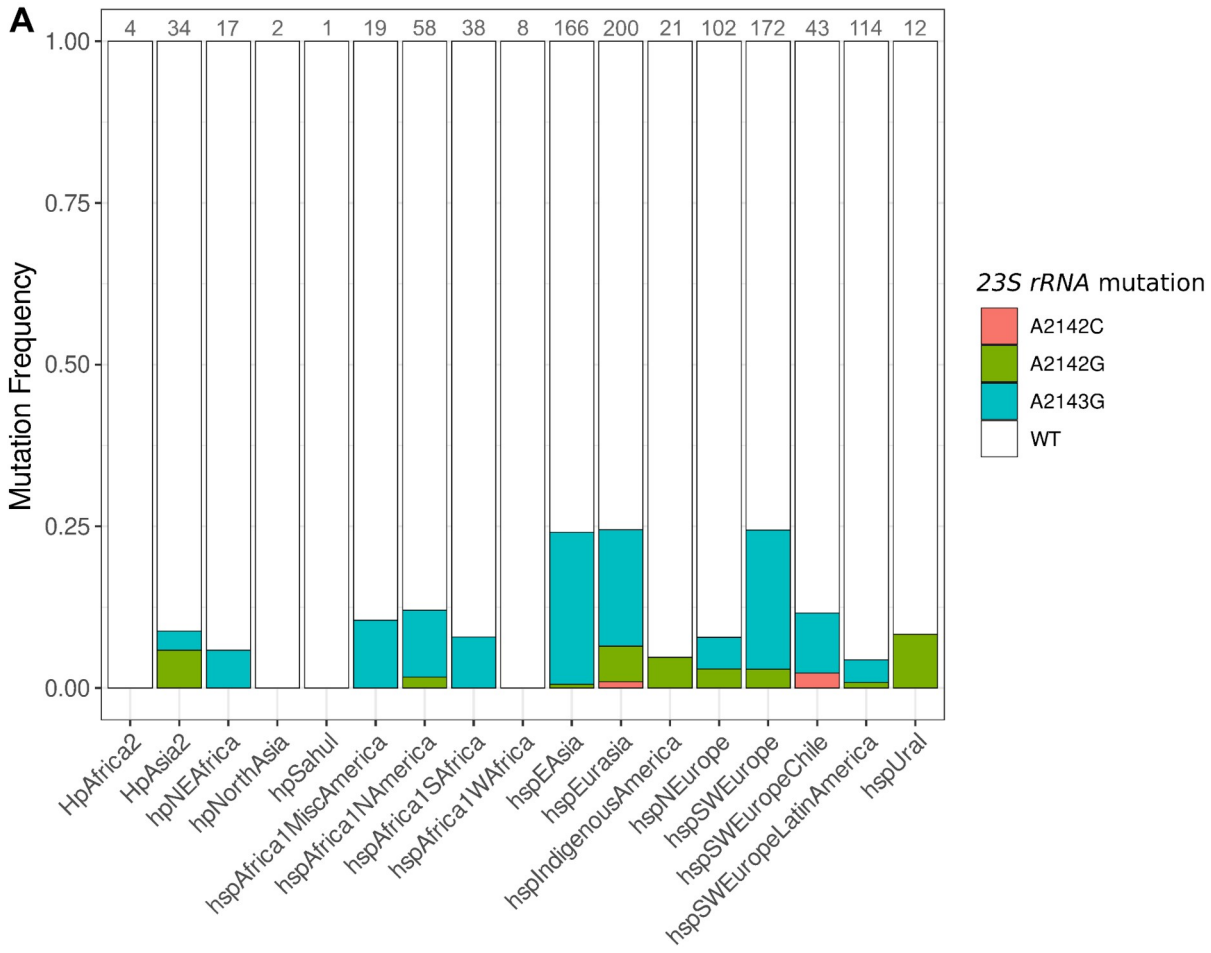
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58
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0.50
0.25
0.00
Mutation Frequency
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HpAsia2
hpNEAfrica
hpNorthAsia
hpSahul
hspAfrica1MiscAmerica
hspAfrica1NAmerica
hspAfrica1SAfrica
hspAfrica1WAfrica
hspEAsia
hspEurasia
hspIndigenousAmerica
hspNEurope
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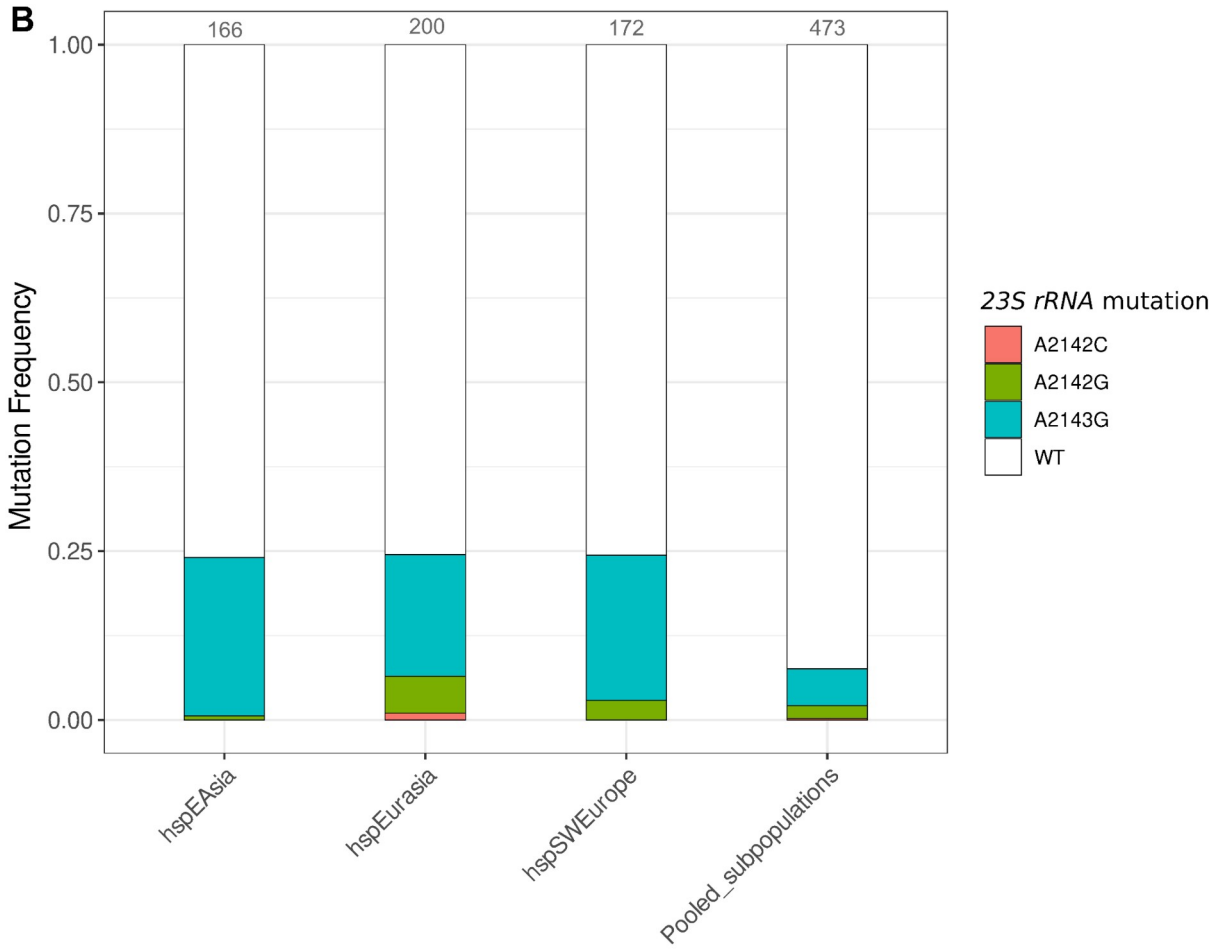
23S rRNA mutation
A2142C
A2142G
A2143G
WT

7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Mutation Frequency
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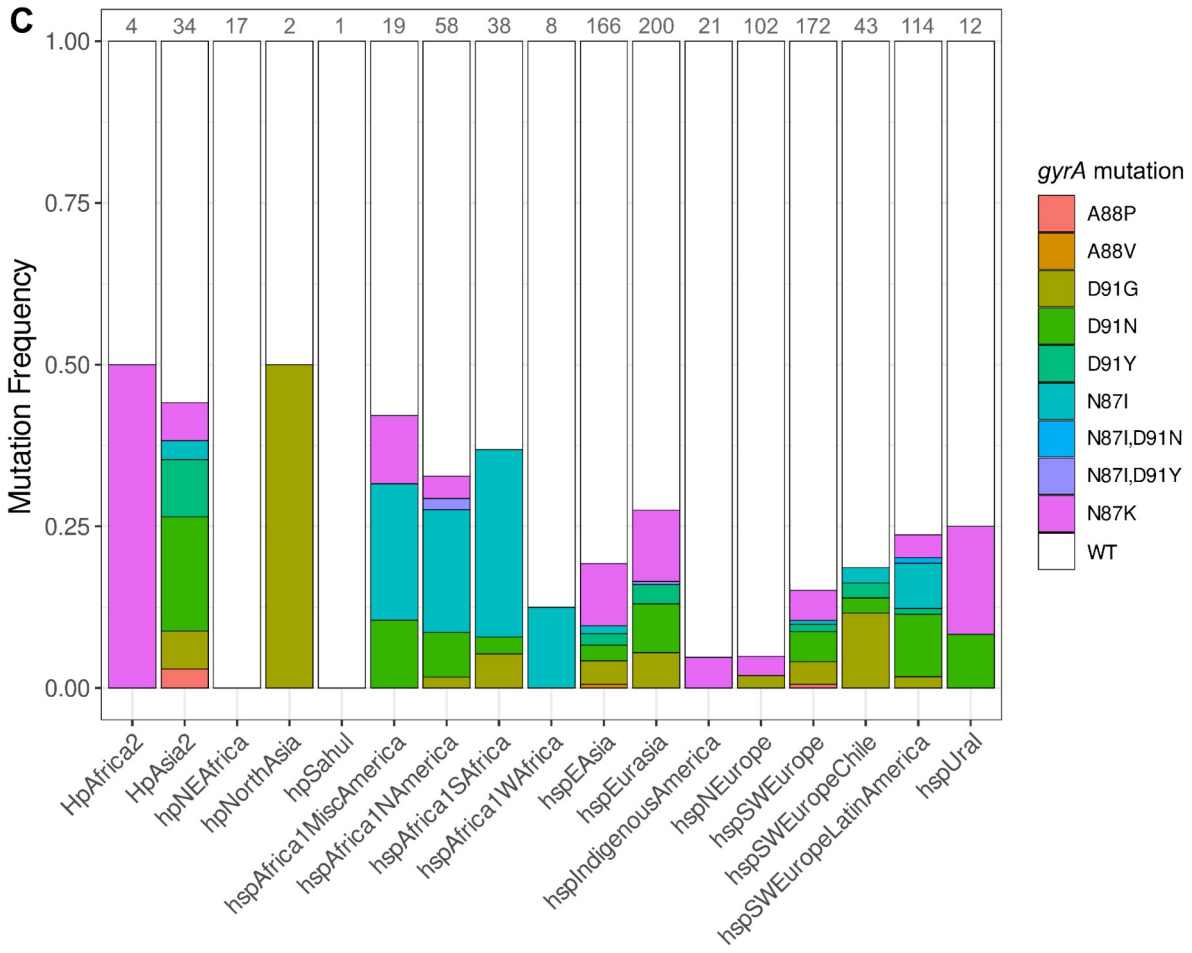
hspEurasia
hspSWEurope
Pooled_subpopulations
23S rRNA mutation
A2142C
A2142G
A2143G
WT

8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0.75
0.50
0.25
0.00
Mutation Frequency
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HpAsia2
hpNEAfrica
hpNorthAsia
hpSahul
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hspAfrica1NAmerica
hspAfrica1SAfrica
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hspEAsia
hspEurasia
hspIndigenousAmerica
hspNEurope
hspSWEurope
hspSWEuropeChile
hspSWEuropeLatinAmerica
hspUral
gyrA mutation
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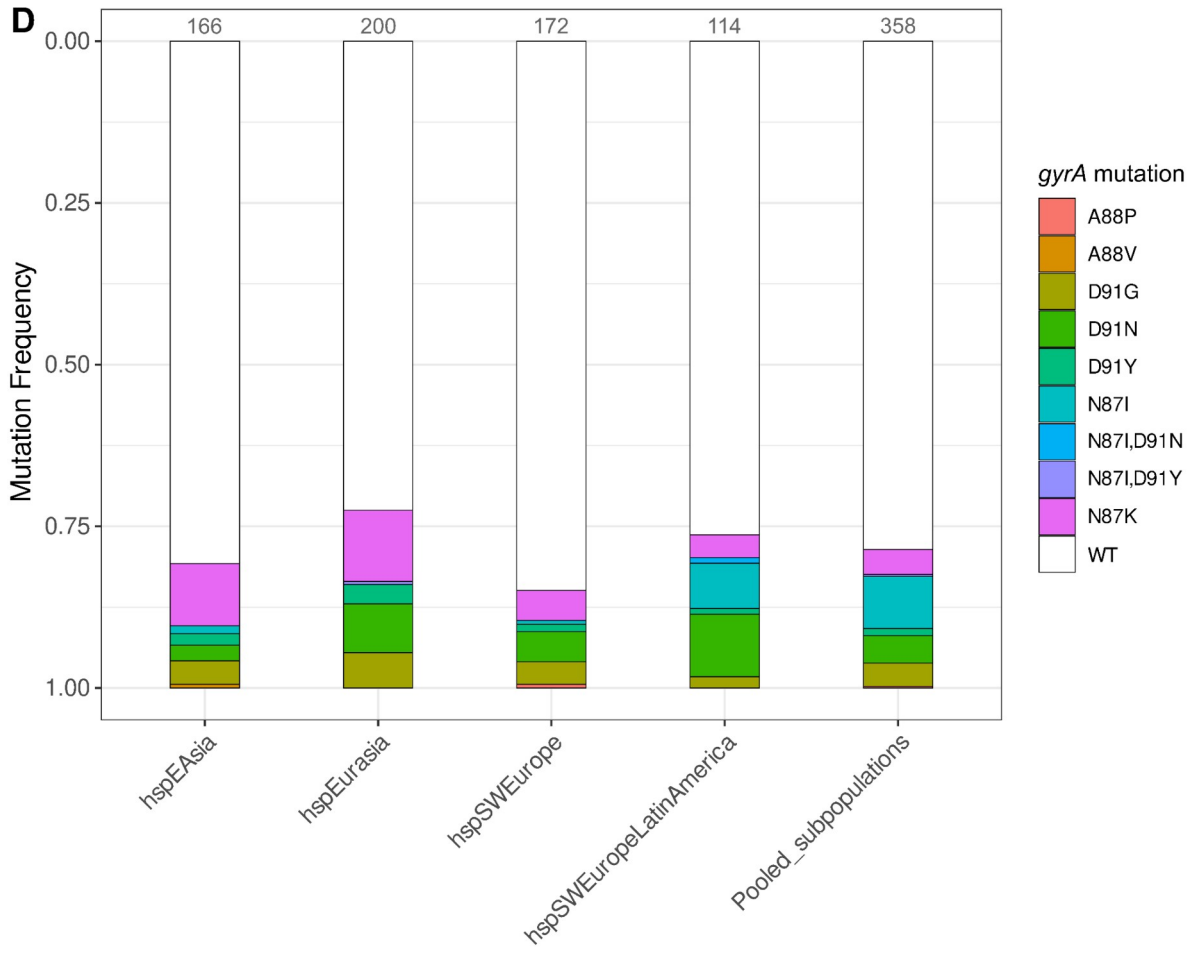
A88V
D91G
D91N
D91Y
N87I
N87I,D91N
N87I,D91Y
N87K
WT

9



Supplementary Figure 2. Proportion of the different *23S rRNA* (A and B) and *gyrA* (C and D) mutations by *H. pylori* population group in the *Hp*GP dataset (n= 1,011).

The number at the top of each bar indicates the number of strains with the mutation in the population group. The total number of strains in the dataset that belong to each of these groups is: HpAfrica2 4 (0·39%), HpAsia2 34(3·36%), hpNEAfrica 17 (1·68%), hpNorthAsia 2 (0·20%), hpSahul 1 (0·10%), hspAfrica1MiscAmerica 19 (1·88%), hspAfrica1NAmerica 58 (5·74%), hspAfrica1SAfrica 38 (3·76%), hspAfrica1WAfrica 8 (0·79%), hspEAsia 166 (16·42%), hspEurasia 200 (19·78%), hspIndigenousAmerica 21 (2·08%), hspNEurope 102 (10·09%), hspSWEurope 172 (17·01%), hspSWEuropeChile 43 (4·25%), hspSWEuropeLatinAmerica 114 (11·28%), hspUral 12 (1·19%). Plots B and D show the most common populations along with the pooled values for the rest of populations.

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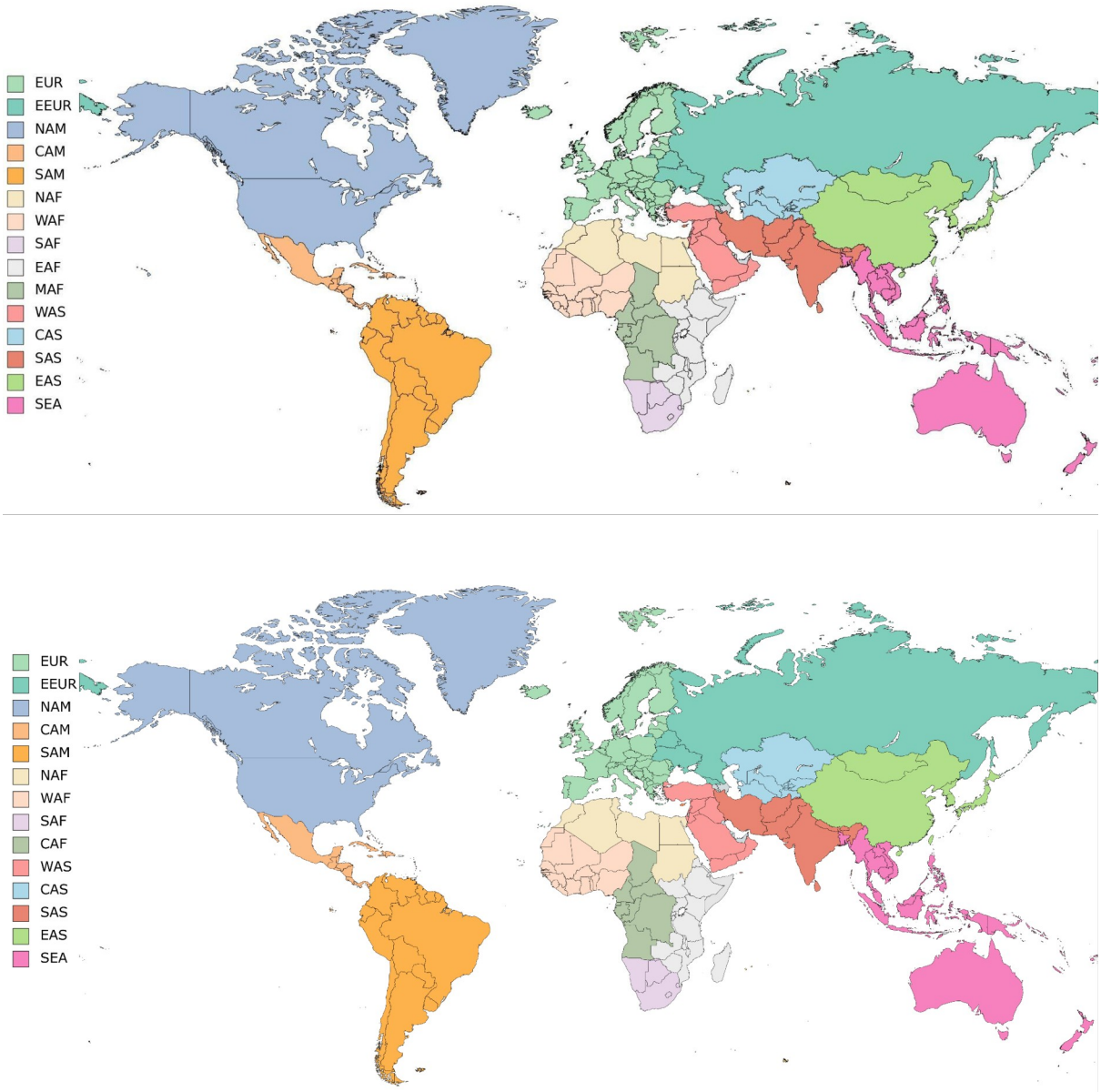

Supplementary Figure 3. Global division by socio-demographic conditions. EUR: Europe; EEUR: Eastern Europe; NAM: North America; CAM: Central America; SAM: South America; NAF: North Africa; WAF: West Africa; SAF: Southern Africa; EAF: East Africa; CAF: Central Africa; WAS: West Asia; CAS: Central Asia; SAS: South Asia, EAS: East Asia; SEA: South-East Asia.

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