RESEARCH ARTICLE

Detection of CYP2C19*2_ allele among Helicobacter pylori - infected patients in two tertiary hospitals of Khartoum, Sudan, 2019 [version 1; peer review: 1 approved with reservations]

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Abstract

Background: CYP2C19*2 has been identified as the most common allelic variant of CYP2C19 affecting the response to Proton pump inhibitors (PPI). This study aims to detect CYP2C19*2 allele in H. pylori-infected Sudanese population, owing its probable effect on H. pylori eradication.

Methods: Antral biopsies was collected from 30 patients attending endoscopy units. Extraction of DNA was performed through QIAamp® DNA Mini Kit. Samples were screened for Urease C (UreC) gene of H. pylori using conventional PCR. Detection of CYP2C19*2 was performed in positive H. pylori samples using Real time-PCR.

Results: The mean age of patients was 40.7 (±20.2 SE). Positive samples for UreC were 24 (80%) samples. Among them, four samples (16.6%) were found positive for CYP2C19*2 allele presence. Gender was found to be statistically associated with the presence of the allele ($p < 0.05$).

Conclusion: This study illustrates that CYP2C19*2 is of modest prevalence among H. pylori-infected Sudanese population. The determination of genotypic and allelic frequencies of CYP2C19 gene among different populations will provide data to be used to personalize treatment according to individual genetic profile, and minimize the possible adverse side effects of CYP2C19 substrates.

Keywords

CYP2C19*2, Helicobacter Pylori, Gastritis, Sudan

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1

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Any reports and responses or comments on the article can be found at the end of the article.

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Abbreviations

GI: gastrointestinal
 H. pylori: Helicobacter pylori
 IM: Intermediate metabolizer
 NM: Normal metabolizer
 PM: Poor metabolizer
 PPI: Proton pump inhibitors
 RM: Rapid metabolizer
 UM: Ultra rapid metabolizer
 UreC: Urease C

Introduction

Helicobacter pylori (H. pylori) is considered the most common bacteria diagnosed in chronically infected stomachs in patients with chronic gastritis.¹ It is infecting more than half of the population worldwide.² In Sudan, it was found in 80% of patients with Barrett's esophagus and gastritis³ and 56.3% among Sudanese children.⁴

H. pylori eradication is inevitably important, as it has been classified as a class 1 human carcinogen by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO).⁵ Stomach cancer in Sudan was among the 10 most common primary sites of cancer.⁶ Moreover, H. pylori is related to chronic gastritis, duodenal and gastric ulcers, and MALT lymphoma.⁷

The first line regimens used are triple and quadruple therapy.⁸ They include proton pump inhibitors (PPI) along with other antibiotics. However, high rate of unsuccessful eradication was reported worldwide,⁹ and the most important causes of treatment failure of H. pylori were found to be clarithromycin resistance and CYP2C19 polymorphism.¹⁰ CYP2C19 allelic variations are considered the keystone and the most addressed pharmaco-genetic factors affecting the response to PPI.¹¹

CYP2C19 gene is a member of the CYP450 gene family, which is located at the 10q24.1–10q24.3 locus of chromosome 10.¹² It is required in metabolizing of several important therapeutic drugs, including PPI, proguanil, propranolol, imipramine, and numerous other drugs.¹³ CYPs' allelic constitution varies according to ethnic and individual variations. This will affect the efficacy of drugs and disease susceptibility.¹⁴

Around 25 genetic variants have been detected in CYP2C19, precisely in the exonic region.¹⁵ CYP2C19 phenotype is classified into ultra-rapid (UM), rapid (RM), normal (NM), intermediate (IM) and poor metabolizer (PM), depending on the allelic constitution of an individual, and affecting the metabolism of a range of xenobiotics.¹¹

CYP2C19 allelic variation affect H. pylori eradication regimen in many ways. Studies showed that lower eradication rates of H. pylori were observed in NM compared to IM and PM.¹¹ Moreover, lower doses of CYP2C19 substrates will be required for patients with IM and PM phenotypes, due to the risk of overexposure and adverse effects of standard doses.¹⁶

CYP2C19*2 has been identified as the most common allelic variant of CYP2C19, and it's considered as the main allele contributing to the PM phenotype.¹² It is located in exon 5, where a splice mutation generates a cryptic splice site, causing the formation of aberrant mRNA, which is translated as non-functional protein.¹⁷ CYP2C19 *3, *4, *5, *6, *7, *8 are other non-functioning alleles, but they are less frequent.¹⁸

PM phenotype which entails carrying two copies of non-functioning alleles is present in about 2-5% of European and African nations, and 15% of Asians.¹⁹ IM phenotype which requires only one copy of a non-functioning allele is present in 25-35% of Europeans and African nations, and 45%-50% of Asians.¹⁹

In Sudan, this allele has not been tackled among H. pylori-infected Sudanese population. Thus, this study aims to detect CYP2C19*2 allele among this population, owing to its probable effect on H. pylori eradication, and the high frequency of this mutant allele in various ethnicities.

Methods

Study population

Convenient sampling of patients visiting endoscopy units of two tertiary hospitals of Khartoum city in the period of May and June 2019 was executed. The study included 30 patients who were undergoing oesophago-gastro-duodenoscopy (OGD), indicated for upper gastrointestinal (GI) symptoms, and accepted to participate in the study. Samples were analyzed and stored at the Virology department of Central laboratory, Ministry of Higher Education and Research, Sudan.

Sample collection

A single antral gastric biopsy was collected from each patient after taking informed verbal consent. A questionnaire composed of three sections; details of sample collection, socio-demographic data, and clinical symptoms and signs related to *H. pylori* history were used to collect patient's information. Samples were collected in phosphate buffer saline medium for reservation and stored at -20°C in 1.5 ml cryo-tubes.

Processing methods

Genomic extraction and primers and probes sequences

Samples were processed and extracted using QIAamp[®] DNA Mini Kit (250) 51306 (QIAGEN, Germany). First, samples were cut into small pieces to decrease the lysis time, then they were transferred into 1.5 ml microcentrifuge tubes. 20 μl of proteinase K was added and samples were incubated at 56°C until the tissue was completely lysed. Brief centrifugation was then performed, followed by adding 200 μl of Buffer AL, mixed by pulse-vortexing for 15 seconds, and incubated at 70°C for 10 minutes. This was followed by adding 200 μl of ethanol (96–100%), which was mixed by pulse-vortexing for 15 seconds, and briefly centrifuged. The mixture then was transferred to QIAamp Mini spin column and centrifuged at $6000 \times g$ (8000 rpm) for one minute. Then QIAamp Mini spin column was placed in a clean 2 ml collection tube, and the remaining filtrate was discarded. 500 μl of Buffer AW1 was then added and centrifuged at $6000 \times g$ (8000 rpm) for one minute, and QIAamp Mini spin column was placed in a clean 2 ml collection tube, and the remaining filtrate was discarded. This was repeated using 500 μl of Buffer AW2, but centrifuged at full speed for three minutes. The QIAamp Mini spin column was then placed in a new collection tube and centrifuged at full speed for one minute. Then the spin column was placed in a 1.5 ml microcentrifuge tube, and 200 μl Buffer AE was added, and incubated at room temperature for one minute, then centrifuged at $6000 \times g$ (8000 rpm) for one minute.

The quantity and quality of the extracted DNA were examined spectrophotometrically. Primers and probes sequences are mentioned in [Table 1](#).

Helicobacter pylori detection

Conventional PCR was performed for the detection of Urease C (UreC) gene in *H. pylori*.²⁰ The reaction mixture was 20 μl comprising of 4 μl of Solis BioDyne Master Mix (5 $\times$ FIREPol[®] Master Mix Ready to Load), 0.5 μl of each forward and reverse primers, 5 μl of template DNA, and 15 μl of H_2O .

DNA amplification was carried out as follows:

1. Denaturation at 94°C for five minutes in the first cycle, followed by annealing for 30 seconds at 65°C .
2. Extension for 30 seconds at 72°C . The extension for the last cycle was increased to five minutes to ensure complete extension of the amplified fragments.
3. Denaturation for 30 seconds at 94°C for a total of 35 PCR cycles. Then the PCR products were resolved by 2% agarose gel electrophoresis. The band size was 297 base pairs.

Real-time PCR for CYP2C19*2 detection

Detection of CYP2C19*2 was performed among positive *H. pylori* samples through Real-time PCR (Genebank No. NG_008384.2). The reaction mixture was 10 μl comprising of 2 μl of Solis BioDyne Master Mix (5 $\times$ HOT FIREPol[®] Probe Universal qPCR Mix), 0.4 μl of each forward and reverse primers, 0.2 μl of the probe, 3 μl of template DNA, and 4 μl of H_2O . Initial activation was at 95°C for five minutes, followed by 15-second denaturation at 95°C , and one minute annealing at 600 for 45 cycles.

Table 1. Primers and probes sequences used in conventional and Real-time PCR.

Target gene	Primers/probes (5'-3')	Product	Reference/GeneBank No.
UreC	F: AAGCTTTTAGGGGTGTTAGGGGTTT R: AAGCTTACTTTCTAACACTAACGC	297	20
CYP2C19*2	F: GCTTGGCATATTGTATCTATACCTT R: GATTCTTGGTGTCTTTTACTTTCT Probe: VIC-ATTTCCAGGAACC-MGB	85	NG_008384.2

Ethical consideration

Informed consent was taken verbally from each patient, and patient's parents in case of minors (below 18 years), and detailed full information about the research purposes and procedures was explained. Verbal consent was performed and approved by the ethics committee due to the cultural stigma in the population regarding the signed procedures as contract-like documents. Also, time and setting of taking the consent was limited, as it was executed after the patient is prepared for the endoscopy procedure.

Ethical approval was obtained from the ethical committee of Central Laboratories, Ministry of Higher education and Research (Ref. No: CL/85/2019). Consent was also taken from hospitals managers and research committee. Patient information was held with a high level of confidentiality.

Statistical analysis

The collected data were entered into Microsoft Excel database and analyzed using Statistical Package for Social Sciences (SPSS) version 23 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were reported as frequencies and percentages for categorical variables, and continuous variables were described as mean $\pm$ standard deviation (SD). Chi-square test was used to test the significant difference among categorical variables, and *p*-value at 0.05 was considered significant.

Results

Socio-demographics of participants

A total of 30 patients were enrolled to participate in the study. Patients were selected from two tertiary hospitals of Khartoum city from endoscopy sessions. All patients were performing OGD for various indications, such as alarming upper GI symptoms and refractory GI symptoms. All patients had not taken any antibiotics or PPI in the last month.

The mean age of patients was 40.7 (± 20.2 SE). Ranging from 9 to 89 years old. Gender was almost divided equally. More information is mentioned in [Table 2](#).

Clinical characteristics of patients

Patients were mostly suffering from vomiting as the main symptom, followed by epigastric pain, regurgitation, and heartburn, respectively ([Figure 1](#)).

Endoscopic findings were mainly gastritis.³² Duodenal and gastric ulcers were only found in 6.6% and 3.3%, respectively. No patients had a lesion suggestive of malignancy ([Figure 2](#)).

Table 2. Socio-demographics of participants, (n = 30), Khartoum, Sudan.

Variable	n (%)
Gender	
Male	16 (53.3%)
Female	14 (46.7%)
Origin	
Northern states	14 (46.7%)
Western states	5 (16.7%)
Central states	3 (10%)
White Nile state	2 (6.7%)
Missing	6 (20%)
Occupation	
House wife	6 (20%)
Medical	2 (6.7%)
Student	4 (13.3%)
Farmer	2 (6.7%)
Miscellaneous	10 (33.3%)
Not working	5 (16.7%)
Missing	1 (3.3%)
Education	
Illiterate	4 (13.3%)
Primary schooling	2 (6.7%)
Secondary schooling	7 (23.3%)
University	13 (43.3%)
Missing	4 (13.3%)

Figure 1. Signs and symptoms of participants, (n = 30), Khartoum, Sudan. SOB: shortness of breath.

Figure 2. Endoscopic findings of participants, (n = 30), Khartoum, Sudan.

Only seven of the participants had known *H. pylori* profiles, which five of them were previously found to be positive for the infection. Stool antigen test and serology were the test of choice for their investigations. Only two patients were treated for the infection.

H. pylori genome and CYP2C19*2 allele detection

Out of the 30 investigated biopsies, 24 (80%) were found positive for *UreC* gene of *H. pylori*. Only those 24 *UreC* positive samples were explored for CYP2C19*2 allele. Four samples (16.6%) were found positive for the allelic mutation.

The four samples were all of female gender, originally from Northern state, and residing in Khartoum. Their mean age was 42.5 (± 22 SD), ranging between 21-74 years old. Three of them showed endoscopic appearance of gastritis, and two

of them suffered from epigastric pain. Gender was found to be statistically associated with the presence of the allele ($p < 0.05$) using Chi-square test of significance. Age, origin, and education have shown no association with the presence of the mutant allele.

Discussion

CYP2C19 gene variants have been investigated in different communities including Europeans, Asians, and Africans,²¹ but it has not been well-studied among the Sudanese population. CYP2C19*2 allele is considered the most common allele as reported by many studies, and it accounts for poor metabolism of PPI, which helps in the eradication of *H. pylori*, yet cause many adverse drug effects²²; hence this study aimed at the detection of the CYP2C19*2 allele among *H. pylori*-infected patients, in which 30 patients undergoing OGD for various indications were selected from two tertiary hospitals in Khartoum city. Among them, females were 53.3%, and males were 46.7%. Patients were mostly suffering from vomiting as the main symptom, followed by epigastric pain, regurgitation and heartburn, respectively.

Out of the 30 investigated biopsies, 24 (80%) samples were positive for the Urease C gene of *H. pylori*. Those positive samples were explored for CYP2C19*2 allele and 4 (16.6%) of the samples were positive for the allelic mutation.

Eradication of *H. pylori* is challenging nowadays due to many reasons including antibiotics resistance, poor compliance, high gastric acidity, and CYP2C19 polymorphism.²³ PPI is a main part of the eradication regimen, and the main enzyme involved in PPI metabolism (except Rabeprazole) is CYP2C19; hence PPI effect depends on the genetic variants of CYP2C19.²³

Several studies revealed significant inter-ethnic differences in CYP2C19*2 variants. Approximately similar inferences of our results were reported among Beninese population²⁴ and Zimbabwean population,²⁵ but less frequency occurred among Ghanaian population (6%),²⁶ Tunisian population (9%),²⁷ and Egyptians (4%).²⁸ Significantly higher frequencies were reported among Japanese (19-23%), Chinese (15%), and Koreans (13%).¹²

Our study reveals a significant association between gender and CYP2C19*2 allele detection ($p < 0.05$). This is consistent with a study done among the Korean population which showed that females had significantly lower metabolic rates than males ($p < 0.0001$), but such a gender difference was not reported among Swedes.²⁹ Caucasians also showed no evidence of gender difference.³⁰ In this study, neither age nor ethnicity was found to be associated with allelic variant presence ($p > 0.05$), but worth noting that all of the positive samples were originally from the Northern state of Sudan, which are considered originating from Arab ancestry. This is inconsistent with a study was done in Sudan in 2018,³¹ showing a significant association with ethnicity ($p = 0.048$), but Arabs were also found to be the highest ethnicity to possess the mutant allele.

The findings of our study have to be seen in the light of some limitations. The sample size was small due to many reasons such as the refusal of some patients to be part of the study and the cost and unavailability of the materials used in the detection of CYP2C19*2 allele.

Conclusion

Yet, this study illustrates that CYP2C19*2 is of modest prevalence among *H. pylori*-infected Sudanese population. Physicians in Sudan should consider this allele as a determinant of suitable drug dosage, which would improve the regimen's effectiveness. The determination of genotypic and allelic frequencies of CYP2C19 gene among different populations will provide data to be used to personalize treatment according to individual genetic profile, and minimize the possible adverse side effects of CYP2C19 substrates.

Data availability

Underlying data

NCBI GenBank: *H. pylori* samples through Real-time PCR, https://www.ncbi.nlm.nih.gov/nucleotide/NG_008384.2.

Figshare: Detection of CYP2C19*2 allele among *Helicobacter pylori*-infected patients in two tertiary hospitals in Khartoum-Sudan: <https://doi.org/10.6084/m9.figshare.14333138.v1>.³²

This project contains the following underlying data:

- DATA.xlsx

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

Authors' contributions

Drs. Abbas and Malik conceived, designed, acquired, and analyzed the data. Drs. Sulieman and Enan participated in its design and coordination. All authors have read the article critically and approved the final manuscript.

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General:

In this study, the authors evaluated the rate of CYP2C19*2 allele in *H. pylori* infected Sudanese population. In this study, authors showed that 16.6% of patients have CYP2C19*2 allele.

Major comments:

1. Serious problem of this study is loss of sample power. Therefore, it is unclear whether 16.6% of Sudanese population have CYP2C19*2 allele.
2. Authors should detect CYP2C19 *3 and *17 alleles among this population.
3. Please use *H. pylori* in italic.
4. Why did authors use UreC gene for detection of *H. pylori* infection?
5. In general, most of patients infected with *H. pylori* have chronic gastritis. Why 30% in this study?
6. In Sudan, it was found in 80% of patients with Barrett's esophagus and gastritis (ref 3) and 56.3% among Sudanese children (ref 4). However, there is no data about Barrett's esophagus in this study.
7. CYP2C19 gene variants have been investigated in different communities including Europeans, Asians, and Africans, but it has not been well-studied among the Sudanese population. Please compare rate of CYP2C19 *2 allele with previous studies in the Sudanese population and this study.
8. 16.6% of patients have CYP2C19*2 allele. How about rates of poor metabolizer (*2/*2)?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Upper GI, H. pylori, GERD, Gastric cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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