Polymorphisms of Cytochrome P450 2E1 Gene and Gastric Cancer Risk: A Case Control Study from West Bengal, India

Ghosh Sudakshina 1, Ghosh Soumee 1, Bankura Biswabandhu1, Saha Makhan Lal 2, Panda Chinmay Kumar 3, Chakraborty Subrata1 and Das Madhusudan1*

1Department of Zoology, University of Calcutta, Kolkata, India
2Department of Surgery, Institute of Post Graduate Medical Education and Research, Kolkata, India
3Department of Oncogene Regulation and Viral Associated Human Cancer, Chittaranjan National Cancer Institute, Kolkata, India

Corresponding author: Das M, Department of Zoology, University of Calcutta, 35 Ballygunge Circular Road, Kolkata-700019, West Bengal, India, Tel: +91-09831281756; Fax: +91-33-24614849; E-mail: madhuzoo@yahoo.com

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Abstract

**Background:** RsaI/PstI and Dral polymorphisms of cytochrome P450 2E1 (CYP2E1) gene are regarded as the most common polymorphisms associated with gastric cancer (GC). Very few data of these polymorphisms have been reported from India with regard to GC risk. We evaluated RsaI: -CT053T (rs2031920), PstI: -G1295C (rs3813867) site in the 5’ flanking region, Dral: T7868A (rs6413432) site in intron 6, -G717T rs6413420 and G4768A or V179I rs6413419 polymorphisms of CYP2E1 with GC risk in the population of West Bengal, India.

**Methods:** We enrolled 105 GC patients (cases) and corresponding sex, age and ethnicity matched normal 108 individuals (controls) for the study. Genotyping for rs6413419, rs6413420, rs6413432, rs2031920, rs3813867 of CYP2E1 was performed using DNA sequencing and RFLP analysis.

**Results and conclusion:** Our results suggest that the difference between genotype frequencies of rs3813867 and rs2031920, although not statistically significant but the allele frequencies of rs3813867 (OR=2.29, 95% CI=1.01-5.18, p=0.042) and rs2031920 (OR=2.29, 95% CI=1.01-5.18, p=0.042) showed significant difference between GC and control individuals. This when pooled with smoking augmented GC risk by nearly 4-fold. Therefore, a larger population is needed to be screened to confirm the association of these studied SNPs with GC in India.

**Keywords** Gastric cancer; Cytochrome P4502E1; SNPs

Introduction

Gastric cancer (GC) is one of the most common cancers of the gastrointestinal (GI) tract. It accounts for nearly 8% of the total cancer cases and results in 10% of the overall cancer related deaths. More than 70% of new cases of GC are reported to occur in the developing countries [1]. Although the exact mechanisms of gastric carcinogenesis are still unknown, yet it has been hypothesized to be caused by the interplay of both environmental and genetic factors which differs among different ethnic groups, gender, age and habitual behaviours [2-5]. Earlier epidemiological studies showed the role of smoking, drinking and H pylori infection towards the development of GC [6,7]. However, only a small section of the people exposed to these environmental factors develops GC in the long run, which is indicative of the fact that host genetic factors may also play critical role in gastric carcinogenesis. Polymorphisms of several genes associated with GC risk have been identified worldwide. Of them, cytochrome P4502E1 (CYP2E1) gene encoding the metabolizing enzyme CYP2E1 has been of much importance. It is responsible for the metabolic activation of various carcinogens, such as benzene, vinyl chloride and N-nitrosophenolamines and hence related to cancer threat [8-10]. The activity of this ethanol-inducible enzyme varies with several single nucleotide polymorphisms (SNPs) in the gene encoding this enzyme. For instance, RsaI/PstI polymorphisms, which are in complete linkage disequilibrium (LD), in the 5’-flanking promoter region of CYP2E1 are reported to affect its transcriptional activation [11]. However, the results are controversial. In contrast, the Dral polymorphisms have been found to be associated with only enhanced transcription [12]. RsaI/PstI and Dral polymorphisms are regarded as the most common and influential polymorphisms in CYP2E1 [12] and have been studied with various cancer risks [13-17]. But how the genetic variations of CYP2E1 can elevate the GC risk remains elusive. Moreover, to the best of our knowledge till date, very few data of this gene with regard to GC risk has been reported from India. Thus, our study was aimed to find out the association of CYP2E1 polymorphisms (rs6413419, rs6413420, rs6413432, rs2031920, rs3813867) with GC risk in the population of West Bengal, India.

Subjects and Methods

Patients and control samples

One hundred and five GC cases were recruited from the Department of Surgery, Institute of Post Graduate Medical Education and Research (IPGME and R), Kolkata, West Bengal, India from December 1, 2012 to April 30, 2015. All the individuals enrolled in our study were Bengali. Patients who were newly diagnosed with GC without any other chronic disease and histopathologically confirmed were included. According to histology, the gradations of tumour tissue samples were done using Lauren's classification [18]. One hundred and eight age, sex and ethnicity matched healthy control subjects who neither had cancer nor any familial history of neoplasms were selected.
from the same geographical region and socioeconomic status. Their non-cancer status was confirmed by medical examinations including radiographic examinations. Ethical approval for this study was given by the institutional ethics committee of Institute of Post Graduate Medical Education and Research (IPGME and R), Kolkata, West Bengal, India. A signed informed consent was taken from each of the participants. Each individual participating in the study was interviewed for their lifestyle, socio-demographic characteristics, family history of cancer or any other chronic diseases, habitual behaviors like smoking, drinking and dietary habits and physical activity.

**Body mass index (BMI)**

Height and weight were measured in both patients and controls wearing light clothing and no shoes, to the nearest 0.1 cm and 0.1 Kg, respectively. BMI was calculated with the standard formula: 

\[
BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}
\]

**Blood collection and DNA extraction**

Whole blood (~5 mL) samples were taken from all subjects and collected in separate tubes (contain EDTA, 0.5 M). Genomic DNA was extracted using the DNA extraction kit (QIAamp Blood Kit, QIAGEN, Hilden, Germany) according to the manufacturer’s instruction.

**PCR analysis and direct sequencing**

Five SNPs (rs6413419, rs6413420, rs6413432, rs2031920, rs3813867) of CYP2E1 gene were amplified using specific primers by polymerase chain reaction (PCR). The primers used for each of the amplifications were described in Table 1. PCR amplification was done in a 30 μl volume containing 100 ng of DNA, 0.5 μM of each primer, 0.2 mM of deoxyribonucleotide triphosphate mix, (Invitrogen Carlsbad, CA, USA), 1.5 mM magnesium chloride, 1x buffer and 2.5 Unit Taq Polymerase (Invitrogen). PCR conditions were as follows: denaturation at 94°C for 3 min followed by 44 cycles of denaturation for 30 s, annealing at 58°C-60°C for 30 s, extension at 72°C for 45 s and final extension at 72°C for 5 min. PCR products were subjected to direct DNA sequencing. For rs6413419 and rs6413420, forward and reverse strand sequencing was carried out using the big dye terminator kit (Applied Biosystems, Foster City, CA, USA) on an automated DNA capillary sequencer (Model 3700; Applied Biosystems).

| SNPs (rs number) | Sequence (5’ 3’) | Digestion pieces (restriction enzyme) | Amplicon Length |
|-----------------|------------------|----------------------------------------|-----------------|
| rs6413419       | F: CTCAAACAGGTTCAGACATTCAAC R: GTTGTAGCTGATGAAAGAAAG | Allele T: 867 | 347 bp |
| rs6413420       | F: AACATGTTCCGATGTTGTTG R: ATGATGGAAGCGGGAAAG | Allele A: 509, 308 (Dra1) | 421 bp |
| rs6413432       | F: AGGCTGCTGAGTTCTGGAAG R: TTCAATGGTCCCCTAGTGAC | Allele C: 413 | 867 bp |
| rs3813867       | F: CCAGTGGAGTCTACATTTGTCG R: TTCAATGTGGTCTTAACTTG | Allele A: 413 | 413 bp |

Table 1: Primer sequences and restriction enzymes used for detection of CYP2E1 gene polymorphisms.

**Statistical analysis**

For each SNP, the genotypic data were analyzed by using multivariate logistic regression model. The demographic variables and life style habits (smoking and alcohol consumption) between cases and controls were compared by t-tests (for continuous variables) and chi-square tests (for categorical variables). Hardy-Weinberg equilibrium of each SNP was examined using a χ² test. Next, unconditional logistic regression model was used to evaluate the risk of GC with regard to smoking status, alcohol consumption and BMI. All the tests were done using GraphPad InStat software (GraphPad InStat software, San Diego, CA) and SNPPassoc version 1.81 software (Catalan Institute of Oncology, Barcelona, Spain). Linkage disequilibrium (LD) pattern was analyzed using Haploview 4.2.

**Results**

**Characteristics of study participants**

The study was performed with 105 GC patients (78% males and 22% females) having mean age of 55.43 ± 10.86 years (range 22–80 years). There was a male predominance of GC frequency compared to females. Based on the anatomical location, 98% of the patients had non-cardia and only 2% had cardia type of GC. Histology revealed the sample population to be of 49% intestinal, 23% diffuse and 28% indeterminate type. Smoking (OR=2.45, 95% CI=1.41-4.26, p=0.001) and alcohol consumption (OR=2.77, 95% CI=1.52-5.06, p=0.001) varied significantly between cases and controls where both were found to independently increase the risk of GC. Only 20% of the cases were _H. pylori_ positive and familial cluster for GC occurrence was not observed in our study Table 2.
Table 2: Clinical characteristics of gastric cancer patients and controls, *At diagnosis.

| Characteristics | Control (n=108) | Case (n=105) | Odds ratio (95% CI) | p value |
|-----------------|----------------|--------------|---------------------|---------|
| *Age (years ± SD) | 53.64 ± 7.88 | 55.43 ± 10.86 |                    | 0.169   |
| Sex             |                |              |                     |         |
| Male            | 89             | 82           |                    |         |
| Female          | 19             | 23           |                    | 0.429   |
| *BMI (kg/m²)    | 23.28 ± 1.97 | 20.55 ± 2.75 |                    | <0.001  |

Anatomical location
- Cardia: 3
- Non-cardia: 102

Histological subtypes of tumour
- Intestinal: 52
- Diffuse: 24
- Indeterminate: 29

Alcohol consumption
- No: 85
- Ever: 23

Cigarette/bidi smoking
- No: 66
- Ever: 42

Out of the 5 SNPs studied, rs3813867 and rs2031920 were found to be strongly in LD Figure 1, as has been reported in other studies of the world population.

There were no significant differences between GC and controls in the distribution of either allelic or genotype frequencies of rs6413419, rs6413420 and rs6413432 Table 3.

However, only the allele frequencies of rs3813867 (PstI) (OR=2.29, 95% CI=1.01-5.18, p=0.042) and rs2031920 (RsaI) (OR=2.29, 95% CI=1.01-5.18, p=0.042) showed significant difference between GC and control individuals Table 3 and Figure 2.

A stratification analysis was conducted to evaluate the effects of interaction of PstI/RsaI with the risk of GC according to smoking status, alcohol consumption status and BMI. The difference between genotype frequencies of rs3813867 and rs2031920, although not statistically significant, yet individuals having C and T alleles respectively who were smokers had nearly 4-fold risk of GC (OR=3.98, 95% CI=1.07-14.73) Table 4.

Figure 1: Linkage disequilibrium (LD) pattern (r²) of the five SNPs in CYP2E1 gene in case and control groups. The LD between the SNPs is measured as r² and shown in the diamond at the intersection of the diagonals from each SNP. r²=0 is shown as white, 0<r²<1 is shown in gray and r²=1 is shown in black.
**Figure 2:** Chromatogram showing the RsaI (a) and PstI (b) heterozygotes.

| Genotype          | Controls (n=108) n (%) | Cases (n=105) n (%) | OR* (95% CI) | p-value |
|-------------------|------------------------|--------------------|--------------|---------|
| CYP2E1 rs6413419  | GG                     | 106 (98.1) 2 (1.9) | 1.00         | 0.628   |
|                   | GA                     | 2 (1.9) 0 (0)      | 1.56 [0.26-9.52] | 1.00 |
|                   | AA                     | 0 (0) 99%          | 1.00 [0.15-6.75] | 1.00 |
| CYP2E1 rs6413420  | GG                     | 102 (94.4) 6 (5.6) | 1.00         | 0.741   |
|                   | GA                     | 6 (5.6) 97%        | 1.40 [0.47-4.19] | 0.73   |

**Table 3:** Genotype and allele frequencies of CYP2E1 and association with gastric cancer risk. *Odds ratio were adjusted for age, sex, BMI, alcohol and smoking status.

| Exposure          | Status           | Genotypes | Control (n=108) | Case (n=105) | OR (95% CI)* | P value |
|-------------------|------------------|-----------|----------------|--------------|--------------|---------|
| rs3813867(PstI)   | Smoking          | GG        | 60             | 38           | Reference: (0.19-3.35) | 0.79    | 0.748   |
|                   | Smoker           | GG        | 39             | 49           | Reference: (1.07-14.73) | 3.98    | 0.019   |
|                   | Alcohol          | GG        | 80             | 59           | Reference: (0.20-3.76) | 0.86    | 0.844   |
|                   | Alcoholic        | GG        | 19             | 28           | Reference: (0.73-8.86) | 2.54    | 0.135   |
|                   | Both non-smoker  | GG        | 6              | 35           | Reference: (0.25-13.55) | 1.83    | 0.549   |
|                   | Both smoker      | GG        | 19             | 25           | Reference: (0.58-7.60) | 2.09    | 0.257   |
|                   | BMI <22          | GG        | 23             | 53           | Reference:  | 0.587   |
| rs2031920 RsaI    | Smoking          | CC        | 6              | 38           | Reference: (0.19 - 3.35) | 0.79    | 0.748   |
|                   | Smoker           | CC        | 39             | 49           | Reference: (1.07 - 14.73) | 3.98    | 0.019   |
|                   | Alcohol          | CC        | 80             | 59           | Reference: (0.20-3.76) | 0.86    | 0.844   |
|                   | Alcoholic        | CC        | 19             | 28           | Reference: (0.73-8.86) | 2.54    | 0.135   |
Discussion

The genes that encode the CYP family of enzymes are highly polymorphic and thus lead to inter individual variation in enzyme activity. The activation of various carcinogens like polycyclic aromatic hydrocarbons, nitrosamines and heterocyclic amines involves the active role of these enzymes. An increased risk of GC associated with CYP2E1 polymorphisms that can modify the effects of environmental factors have now been confirmed in many populations throughout the world i.e. Korean [19,20], Chinese [21] and Taiwanese [22]. This enzyme also reduces oxygen molecule to highly active form, which is carcinogenic, and may lead to cancer development [23]. Previous research showed that CYP2E1 gene polymorphisms may be a cause of development of GC [24-29]. The most widely studied SNPs of CYP2E1 are Rsal: -C1053T (rs2031920), PstI -G1295C (rs3813867) site in the 5’ flanking region, DraI: T7668A (rs6413432) site in intron 6. -G 71T rs6413420 and G4768A or V179I rs6413419 [30-33]. The present study was aimed to find out the association between these five most studied SNPs of CYP2E1 and GC incidence in the population of West Bengal, India. We screened 105 GC patients and 108 normal individuals for the study. Rsal/PstI and DraI polymorphisms are regarded as the most frequent and powerful polymorphisms in CYP2E1 that are considered to enhance transcription [12]. Our results suggest that the difference between genotype frequencies of rs3813867 and rs2031920, although not statistically significant but the allele frequencies of rs3813867 (OR=2.29, 95% CI=1.01-5.18, p=0.042) and rs2031920 (OR=2.29, 95% CI=1.01-5.18, p=0.042) showed significant difference when combined with smoking increased the risk of GC by nearly 4-fold. However, study with larger sample may contribute to a better understanding towards the association of GC with the studied SNPs.

Table 4: Interaction between CYP2E1 rs3813867, rs2031920 polymorphisms and smoking and alcohol consumption in gastric cancer, Odds ratio were adjusted for age, sex, BMI, alcohol and smoking status.

| Smoking+Alcohol | Both non-smoker and non-alcoholic | CC | CT | 64 | 2 | 35 | 2 | Reference: (0.25-13.55) | 1.83 | 0.549 |
|----------------|----------------------------------|----|----|----|----|----|----|--------------------------|------|-------|
| Both smoker and alcoholic | CC | CT | 19 | 4 | 25 | 11 | Reference: (0.58-7.60) | 2.09 | 0.257 |
| BMI | <22 | CC | CT | 23 | 4 | 53 | 14 | Reference: (0.22-14.79) | 1.79 | 0.587 |

Conclusion

We conducted the first study of association between CYP2E1 polymorphisms and the risk of GC from West Bengal, India. Our results suggest that the difference between genotype frequencies of rs3813867 and rs2031920, although not statistically significant but the allele frequencies of rs3813867 and rs2031920 showed significant difference between GC and control individuals. This when combined with smoking increased the risk of GC, by nearly 4-fold. However, study with larger sample may contribute to a better understanding towards the association of GC with the studied SNPs.

Conflict of Interest

We have no conflict of interest to declare.

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