Cancer Genetics 238 (2019) 23–30

Contents lists available at ScienceDirect

Cancer Genetics

journal homepage: www.elsevier.com/locate/cancergen

Original Article

# Variants in *COL6A3* gene influence susceptibility to esophageal cancer in the Chinese population

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ARTICLE INFO

*Article history:*
Received 22 April 2019
Revised 4 July 2019
Accepted 11 July 2019

*Keywords:*
*COL6A3*
Esophageal cancer
Genetic models
Polymorphism
Variants

ABSTRACT

Esophageal cancer (EC) is a frequent malignant tumor in our world, and has a highly morbidity and mortality. It was reported that genetic factors play vital roles in its pathogenesis. Here, we performed a case - control study to evaluate the *COL6A3* genetic variants and EC risk in a Chinese Han cohort. All subjects were genotyped with the Agena MassARRAY platform. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression after adjusting age and gender. We found that rs6720283 ($G > A$) allele had significantly enhanced EC risk (OR = 1.32, 95% CI = 1.11 alculate $p = 0.002$). Stratified analysis was performed by gender, age, alcohol drinking, BMI, TNM stage and lymph node metastasis, the results showed that rs7436, rs115510139 and rs6720283 were significantly associated with the risk of EC in different groups (all $p < 0.05$). Besides, no statistical significant was found between the *COL6A3* gene polymorphisms and clinicopathological parameters such as TNM stage and lymph node metastasis among EC patients ($p > 0.05$). In conclusions, our study found that *COL6A3* variants were associated with risk of EC in the Chinese population.



## Instruction

Esophageal cancer (EC) is considered a most common gastrointestinal malignant cancer in our world [1]. It has a highly morbidity and mortality, more than 450,000 new cases of EC were diagnosed, and about 400,000 patients were died in each year [2]. According to histological type, EC was classified two different forms, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) [3]. Several reports revealed that ESCC is the main histological subtype of EC in developing countries [4]. Epidemiological and etiological researches suggested that various environment and cultural factors, including smoking, heavy alcohol drinking, infection of bacteria or virus, dietary habits and nutritional deficiencies were associated with EC risk [5–7]. Recently, more and more researches showed that genetic variations, especially gene polymorphisms were significantly contributed to EC risk [8–10].

In China, esophageal cancer was the third common diagnosed cancer and the fourth contributing to cancer death [11]. Currently, several Genome Wide Association Studies (GWAS) have demonstrated that genetic variations were correlated with EC risk in Chinese population [7,12,13]. Hou et al. identified three SNPs including rs132131, rs4444235 and rs6687758 were associated with an improved esophageal cancer in Chinese population [6]. Liu et.al found that Flap endonuclease-1 (*FEN1*) rs174538 $G > A$ might influence personal susceptibility to esophageal cancer in China [14]. Liu et.al also suggested that TT + CT genotype of *XIAP* rs8371 and rs9856 were significantly reduced the risk of esophageal cancer in a Chinese population [15]. *COL6A3* (alpha3), which located in chromosome 2q37, confirmed that the variation of *COL6A3* was correlated with obesity in human [16]. In the current study, six SNPs including rs1050785, rs7436, rs13032404, rs115510139, rs2645765 and rs6720283 were selected from *COL6A3* gene. To our knowledge, this was the first time to demonstrate the role of these SNPs among *COL6A3* gene in Chinese population esophageal cancer.

In the present case-control study, we investigated the relationship between *COL6A3* variations and the risk of esophageal cancer

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https://doi.org/10.1016/j.cancergen.2019.07.003
2210-7762/

**Table 1**
Characteristics of EC patients and healthy controls.

| Variables | Cases ($n = 508$) No. (%) | Controls ($n = 497$) No. (%) | $p$ |
|---|---|---|---|
| Age, year (mean ± SD) | 63.94 ± 9.25 | 64.05 ± 7.89 | 0.837 |
| Age, years | | | |
| ≤ 63 | 239 (47.05) | 250 (50.30) | |
| > 63 | 269 (52.95) | 247 (49.70) | |
| Gender | | | 0.990 |
| Male | 377 (74.21) | 369 (74.25) | |
| Female | 131 (25.79) | 128 (25.75) | |
| Smoking status | | | |
| Yes | / | 123 (24.75) | |
| No | 458 (90.16) | 109 (21.93) | |
| Information loss | 50 (9.84) | 265 (53.32) | |
| Alcohol drinking | | | |
| Yes | 233 (45.87) | 101 (20.32) | |
| No | 265 (52.17) | 106 (21.33) | |
| Information loss | 10 (1.97) | 290 (58.35) | |
| BMI | | | |
| < 24 | 415 (81.69) | 109 (21.93) | |
| ≥ 24 | 73 (14.37) | 123 (24.75) | |
| Information loss | 20 (3.94) | 265 (53.32) | |
| TNM stage | | | |
| *I*+II | 225 (44.29) | | |
| III+IV | 142 (27.95) | | |
| Lymph node metastasis | | | |
| No | 181 (35.63) | | |
| Yes | 175 (34.45) | | |

$p$ values were calculated from $\chi 2$ test/Fisher's exact test.
*$p<0.05$ indicates statistical significance.

in the Chinese population, which can provide a theoretical basis for early diagnosis with esophageal cancer patients.

## Materials and methods

### *Study subjects*

A total of 1015 subjects including 508 patients and 497 healthy controls were recruited from Shaanxi Provincial Cancer Hospital, Xi'an, Shaanxi Province. All participators were unrelated Chinese Han population. Among them, 508 patients were newly histopathological confirmed and diagnosed with esophageal cancer. Patients who suffered from any vital organ dysfunction, a history of another tumor cancer or received radiotherapy and chemotherapy treatment were excluded. The 497 healthy controls who took part in health check in the hospital were randomly selected. The inclusion criteria included a lack of history of cancer, infectious disease, and healthy controls were matched to the cases by gender and age. According to the American Joint Committee (AJCC) on cancer classification and the Union for International Cancer Control (UICC), the tumor node metastasis (TNM) system was used to classify tumors. 225 patients were between stage I-II and 142 patients were between stages III-IV. At the same time, we observed 175 patients with lymph node metastasis and 181 patients with negative lymph node metastasis (Table 1). We collected 5 ml blood samples from each subject, and stored at −80 °C until used for DNA extraction. The protocol of the present study was approved by the clinical investigate ethical committee of the same hospital and all procedures were performed in compliance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### *Genotype analysis*

Genomic DNA of all subjects were extracted from peripheral blood samples using GoldMag Genomic DNA purification kit (GoldMag Co. Ltd. Xi'an city, China), following the manufacturer's instructions. DNA concentration and purity were assessed with a NanoDrop 2000 platform (Thermo Fisher Scientific, Waltham, MA, USA). Six candidate SNPs in the *COL6A3* gene were selected from the 1000 Genomes Project data (http://www.internationalgenome.org/) with minor allele frequency > 0.05. In order to determine the candidate SNP genotype polymorphism, the PCR amplification and extension primers were designed by Agena Bioscience Assay Design Suite V2.0 software (https://agenacx.com/online–tools/). According to the manufacturer's protocol, the MassARRAY Nanodispenser and MassARRAY iPLEX platform (both from Agena Bios 95% Clence, San Diego, CA, USA) were used to genotype the SNPs. Data analysis were further performed by Agena Bioscience TYPER version 4.0 software.

### *Statistical analysis*

Statistical analysis was conducted using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). We applied Chi–square test to evaluate whether the genotype frequency of healthy controls were in conformity with the Hardy-Weinberg equilibrium (HWE). Odds ratios (ORs) and 95% confidence intervals (CIs) were implemented in order to evaluate the correlation between *COL6A3* polymorphism and EC risk using multivariate logistic regression analysis and adjusting by gender and age. We also used four different genetic models to consider the susceptibility of EC. Moreover, we calculated the stratification analysis to assess the correlation between *COL6A3* polymorphisms and the risk of EC. Haploview 4.2 software was performed to construct the haplotypes of *COL6A3* gene. For all statistical tests, $p$ value < 0.05 was considered statistically significant.

## Results

### *Baseline characteristics*

In this study, 508 EC patients including 377 males and 131 females were recruited. The mean age was 63.94 ± 9.25 years old. During the same time, we recruited 497 healthy control subjects including 250 meals and 247 females. The mean age of controls were 64.05 ± 7.89 years old. No significant statistical difference

**Table 2**
Basic characteristics and allele frequencies among *COL6A3* SNPs.

| SNP | Chr | Allele | MAF | | HWE *p*–Value | OR (95% CI) | $P^a$ |
|---|---|---|---|---|---|---|---|
| | | | Case | Control | | | |
| rs1050785 | 2 | G/T | 0.51 | 0.49 | 0.858 | 1.06 (0.89–1.26) | 0.533 |
| rs7436 | 2 | A/T | 0.17 | 0.18 | 1.000 | 0.96 (0.76–1.21) | 0.731 |
| rs13032404 | 2 | A/G | 0.38 | 0.36 | 0.119 | 1.08 (0.90–1.29) | 0.415 |
| rs115510139 | 2 | A/T | 0.52 | 0.49 | 0.472 | 1.12 (0.94–1.33) | 0.211 |
| rs2645765 | 2 | A/G | 0.28 | 0.30 | 0.451 | 0.93 (0.77–1.13) | 0.476 |
| rs6720283 | 2 | A/G | 0.52 | 0.45 | 0.650 | 1.32 (1.11–1.57) | 0.002* |

CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency, OR, odds ratio; SNP, single nucleotide polymorphism.
*Sites with HWE, $p < 0.05$, are excluded.
$P^a$ values calculated with two–sided $\chi 2$.
*$p^a < 0.05$ indicates statistical significance.

**Table 3**
The association between six SNPs within the *COL6A3* gene and the risk of esophageal cancer.

| SNP | Model | Genotype | Cases | Controls | OR (95%CI) | $p^a$ |
|---|---|---|---|---|---|---|
| rs1050785 | Co–dominant | G/G | 124 | 126 | 1 | |
| | | G/T | 252 | 251 | 1.02 (0.75–1.38) | 0.892 |
| | | T/T | 132 | 120 | 1.12 (0.79–1.59) | 0.537 |
| | Dominant | G/G | 124 | 126 | 1 | |
| | | G/T – T/T | 384 | 371 | 1.05 (0.79–1.40) | 0.727 |
| | Recessive | G/G – G/T | 376 | 377 | 1 | |
| | | T/T | 132 | 120 | 1.10 (0.83–1.47) | 0.510 |
| | Log–additive | – | – | – | 1.06 (0.89–1.26) | 0.537 |
| rs7436 | Co–dominant | T/T | 347 | 335 | 1 | |
| | | T/A | 147 | 147 | 0.97 (0.73–1.27) | 0.805 |
| | | A/A | 14 | 14 | 0.90 (0.43–1.89) | 0.777 |
| | Dominant | T/T | 347 | 335 | 1 | |
| | | T/A– A/A | 161 | 162 | 0.96 (0.74–1.25) | 0.761 |
| | Recessive | T/T – T/A | 494 | 482 | 1 | |
| | | A/A | 14 | 15 | 0.91 (0.43–1.90) | 0.797 |
| | Log–additive | – | – | – | 0.96 (0.76–1.21) | 0.729 |
| rs13032404 | Co–dominant | G/G | 203 | 195 | 1 | |
| | | G/A | 225 | 246 | 0.88 (0.67–1.15) | 0.345 |
| | | A/A | 79 | 56 | 1.36 (0.91–2.01) | 0.131 |
| | Dominant | G/G | 203 | 195 | 1 | |
| | | G/A – A/A | 304 | 302 | 0.97 (0.75–1.25) | 0.798 |
| | Recessive | G/G – G/A | 428 | 441 | 1 | |
| | | A/A | 79 | 56 | 1.46 (1.01–2.10) | 0.046* |
| | Log–additive | – | – | – | 1.08 (0.90–1.30) | 0.410 |
| rs115510139 | Co–dominant | T/T | 117 | 134 | 1 | |
| | | T/A | 254 | 239 | 1.22 (0.90–1.65) | 0.203 |
| | | A/A | 133 | 122 | 1.25 (0.88–1.78) | 0.208 |
| | Dominant | T/T | 117 | 134 | 1 | |
| | | T/A– A/A | 387 | 361 | 1.23 (0.92–1.64) | 0.157 |
| | Recessive | T/T – T/A | 371 | 373 | 1 | |
| | | A/A | 133 | 122 | 1.10 (0.83–1.46) | 0.521 |
| | Log–additive | – | – | – | 1.12 (0.94–1.33) | 0.209 |
| rs2645765 | Co–dominant | G/G | 254 | 244 | 1 | |
| | | G/A | 208 | 198 | 1.01 (0.78–1.31) | 0.945 |
| | | A/A | 38 | 47 | 0.78 (0.49–1.23) | 0.282 |
| | Dominant | G/G | 254 | 244 | 1 | |
| | | G/A – A/A | 246 | 245 | 0.96 (0.75–1.24) | 0.775 |
| | Recessive | G/G – G/A | 462 | 442 | 1 | |
| | | A/A | 38 | 47 | 0.77 (0.49–1.21) | 0.258 |
| | Log–additive | – | – | – | 0.93 (0.77–1.13) | 0.475 |
| rs6720283 | Co–dominant | G/G | 121 | 149 | 1 | |
| | | G/A | 249 | 250 | 1.23 (0.91–1.65) | 0.178 |
| | | A/A | 137 | 96 | 1.76 (1.23–2.51) | 0.002* |
| | Dominant | G/G | 121 | 149 | 1 | |
| | | G/A – A/A | 386 | 346 | 1.37 (1.04–1.82) | 0.027* |
| | Recessive | G/G – G/A | 370 | 399 | 1 | |
| | | A/A | 137 | 96 | 1.54 (1.14–2.07) | 0.004* |
| | Log–additive | – | – | – | 1.32 (1.11–1.58) | 0.002* |

CI, confidence interval; OR, odds ratio; SNP: single nucleotide polymorphism.
*$p^a < 0.05$ indicates statistical significance.

**Table 4**
The association between the *COL6A3* gene polymorphisms and the risk of esophageal cancer stratified by age.

| SNP | Model | Genotype | ≤63 | | > 63 | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | $P^a$ | OR (95% CI) | $P^a$ |
| rs1050785 | Co–dominant | G/G | 1 | | 1 | |
| | | G/T | 1.01 (0.65–1.56) | 0.965 | 1.07 (0.70–1.64) | 0.741 |
| | | T/T | 1.01 (0.62–1.67) | 0.956 | 1.27 (0.77–2.11) | 0.352 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/T – T/T | 1.01 (0.67–1.52) | 0.956 | 1.13 (0.75–1.69) | 0.554 |
| | Recessive | G/G – G/T | 1 | | 1 | |
| | | T/T | 1.01 (0.66–1.53) | 0.970 | 1.21 (0.80–1.84) | 0.366 |
| | Log–additive | – | 1.01 (0.78–1.29) | 0.955 | 1.13 (0.87–1.45) | 0.356 |
| rs7436 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 1.10 (0.73–1.65) | 0.646 | 0.91 (0.62–1.33) | 0.616 |
| | | A/A | 0.59 (0.22–1.56) | 0.283 | 2.03 (0.51–7.99) | 0.313 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 1.02 (0.69–1.50) | 0.917 | 0.95 (0.66–1.38) | 0.787 |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 0.57 (0.22–1.50) | 0.255 | 2.09 (0.53–8.19) | 0.291 |
| | Log–additive | – | 0.95 (0.69–1.32) | 0.755 | 1.01 (0.72–1.41) | 0.966 |
| rs13032404 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.07 (0.73–1.59) | 0.719 | 0.760 (0.52–1.10) | 0.148 |
| | | A/A | 1.34 (0.74–2.40) | 0.331 | 1.34 (0.77–2.32) | 0.296 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.13 (0.78–1.63) | 0.533 | 0.86 (0.60–1.23) | 0.415 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.29 (0.75–2.22) | 0.367 | 1.56 (0.94–2.60) | 0.086 |
| | Log–additive | – | 1.13 (0.86–1.48) | 0.368 | 1.04 (0.81–1.34) | 0.766 |
| rs115510139 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 1.51 (0.98–2.34) | 0.064 | 0.84 (0.56–1.28) | 0.417 |
| | | A/A | 1.26 (0.76–2.11) | 0.373 | 0.82 (0.50–1.33) | 0.416 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 1.43 (0.94–2.16) | 0.091 | 0.83 (0.56–1.23) | 0.361 |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 0.97 (0.63–1.48) | 0.873 | 0.91 (0.61–1.37) | 0.657 |
| | Log–additive | – | 1.13 (0.88–1.46) | 0.337 | 0.90 (0.71–1.15) | 0.404 |
| rs2645765 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.12 (0.77–1.65) | 0.549 | 0.94 (0.65–1.36) | 0.729 |
| | | A/A | 0.79 (0.40–1.57) | 0.502 | 0.68 (0.36–1.31) | 0.250 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.06 (0.74–1.53) | 0.751 | 0.89 (0.62–1.26) | 0.495 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 0.75 (0.39–1.45) | 0.390 | 0.70 (0.38–1.32) | 0.272 |
| | Log–additive | – | 0.98 (0.74–1.30) | 0.898 | 0.87 (0.66–1.14) | 0.315 |
| rs6720283 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.06 (0.68–1.65) | 0.808 | 1.43 (0.95–2.16) | 0.085 |
| | | A/A | 2.18 (1.30–3.67) | 0.003* | 1.44 (0.88–2.37) | 0.147 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.34 (0.88–2.04) | 0.169 | 1.44 (0.98–2.11) | 0.065 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 2.10 (1.37–3.23) | 0.001* | 1.15 (0.75–1.76) | 0.515 |
| | Log–additive | – | 1.48 (1.14–1.91) | 0.003* | 1.22 (0.95–1.56) | 0.119 |

CI, confidence interval; OR, odds ratio; SNP: single nucleotide polymorphism.
*$p^a < 0.05$ indicates statistical significance.

were observed ($p = 0.837$ and $p = 0.990$), which indicated that our two groups were adequately matched. The basic information of subjects including age, gender, smoking status, alcohol drinking, BMI (body mass index), TNM stage and Lymph node metastasis were summarized in Table 1.

### *Association of COL6A3 genotypes with esophageal cancer risk*

The basic information of candidate SNPs including the position, minor allele frequency (MAF) and Hardy– Weinberg equilibrium (HWE) $p$ value were displayed in Table 2. Frequencies distribution of all candidate SNPs were in agreement with HWE in healthy controls (all $p > 0.05$), which indicates that the genotype frequencies of *COL6A3* SNPs in case and control groups were in equilibrium and our samples were well representation of the population. Furthermore, we estimated the association between the allele frequencies and the risk of EC. The results suggested that rs6720283 ($G > A$) allele had significantly enhanced EC risk (OR = 1.32, 95% CI = 1.11 – 1.57, $p = 0.002$). However, no remarkable changed risk of EC was observed to relate to the other SNPs genotype.

Four genetic models were used to analysis the genotype frequencies of *COL6A3* SNPs, and to evaluated the association between SNPs and the risk of EC. When compared with the G/G genotype, rs6720283 A/A genotype was associated with a statistically improved risk of EC under the co-dominant model (OR = 1.76, 95% CI = 1.23 – 2.51, $p = 0.002$). Similarity, we also found that rs6720283 was significantly increased the risk of EC under the Log-additive model (OR = 1.32, 95% CI = 1.11 – 1.58, $p = 0.002$), the dominant model (OR = 1.37, 95% CI = 1.04 – 1.82, $p = 0.027$) and the recessive model (OR = 1.54, 95% CI = 1.14 – 2.07, $p = 0.004$) (Table 3).

### *Interaction of* COL6A3 *gene polymorphisms and clinicopathological parameters of esophagus cancer*

In order to assess the contribution of demographic and clinicopathological parameters, including gender, age, alcohol drinking,

**Table 5**
The association between the *COL6A3* gene polymorphisms and the risk of esophageal cancer stratified by gender.

| SNP | Model | Genotype | Males | | Females | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | $P^a$ | OR (95% CI) | $P^a$ |
| rs1050785 | Co–dominant | G/G | 1 | | 1 | |
| | | G/T | 0.86 (0.61–1.23) | 0.411 | 1.16 (0.65–2.07) | 0.621 |
| | | T/T | 0.88 (0.59–1.33) | 0.548 | 1.06 (0.54–2.11) | 0.861 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/T – T/T | 0.87 (0.63–1.21) | 0.407 | 1.13 (0.65–1.95) | 0.670 |
| | Recessive | G/G – G/T | 1 | | 1 | |
| | | T/T | 0.97 (0.69–1.36) | 0.871 | 0.97 (0.54–1.73) | 0.914 |
| | Log–additive | – | 0.94 (0.76–1.15) | 0.540 | 1.04 (0.74–1.46) | 0.839 |
| rs7436 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 0.87 (0.64–1.20) | 0.405 | 1.29 (0.75–2.2) | 0.362 |
| | | A/A | 0.70 (0.29–1.69) | 0.425 | 1.75 (0.4–7.63) | 0.456 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 0.86 (0.63–1.17) | 0.325 | 1.32 (0.78–2.23) | 0.295 |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 0.73 (0.30–1.75) | 0.476 | 1.62 (0.38–6.99) | 0.518 |
| | Log–additive | – | 0.86 (0.66–1.13) | 0.278 | 1.30 (0.82–2.05) | 0.264 |
| rs13032404 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 0.90 (0.66–1.22) | 0.493 | 0.83 (0.48–1.41) | 0.487 |
| | | A/A | 1.33 (0.83–2.10) | 0.233 | 1.43 (0.66–3.09) | 0.366 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 0.98 (0.73–1.31) | 0.876 | 0.93 (0.56–1.55) | 0.794 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.40 (0.91–2.16) | 0.124 | 1.59 (0.79–3.23) | 0.196 |
| | Log–additive | – | 1.07 (0.87–1.33) | 0.515 | 1.09 (0.76–1.57) | 0.624 |
| rs115510139 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 1.33 (0.93–1.89) | 0.114 | 1.06 (0.58–1.93) | 0.856 |
| | | A/A | 1.40 (0.94–2.09) | 0.101 | 1.14 (0.56–2.32) | 0.721 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 1.35 (0.97–1.88) | 0.073 | 1.08 (0.61–1.92) | 0.787 |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 1.16 (0.84–1.62) | 0.370 | 1.1 (0.61–1.96) | 0.757 |
| | Log–additive | – | 1.18 (0.97–1.45) | 0.102 | 1.07 (0.75–1.52) | 0.721 |
| rs2645765 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 0.98 (0.72–1.32) | 0.874 | 1.12 (0.66–1.9) | 0.668 |
| | | A/A | 0.61 (0.35–1.06) | 0.078 | 1.45 (0.6–3.51) | 0.410 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 0.90 (0.68–1.21) | 0.488 | 1.18 (0.72–1.94) | 0.518 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 0.62 (0.36–1.05) | 0.075 | 1.38 (0.59–3.23) | 0.461 |
| | Log–additive | – | 0.86 (0.69–1.08) | 0.189 | 1.17 (0.80–1.71) | 0.411 |
| rs6720283 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.29 (0.91–1.83) | 0.150 | 1.07 (0.60–1.90) | 0.829 |
| | | A/A | 1.78 (1.18–2.69) | 0.006* | 1.70 (0.84–3.42) | 0.139 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.43 (1.03–1.98) | 0.032* | 1.23 (0.71–2.12) | 0.456 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.51 (1.07–2.13) | 0.019* | 1.63 (0.90–2.96) | 0.108 |
| | Log–additive | – | 1.33 (1.09–1.64) | 0.006* | 1.29 (0.91–1.82) | 0.155 |

CI, confidence interval; OR, odds ratio; SNP: single nucleotide polymorphism.
*$p^a < 0.05$ indicates statistical significance.

BMI, TNM stage and lymph node metastasis to the risk of EC in the Chinese Han population, stratification analyses were applied to evaluate the potential effect of *COL6A3* gene polymorphisms with EC risk. In the stratified analysis by age. The results indicated that the genotype frequencies of *COL6A3* rs6720283 was associated with a significantly increased risk of EC under the co-dominant model (OR = 2.18, 95% CI = 1.30 – 3.67, $p = 0.003$) the recessive model (OR = 2.10, 95% CI = 1.37 – 3.23, $p = 0.001$) and the Log- additive model (OR = 1.48, 95% CI = 1.14 – 1.91, $p = 0.003$) in patients aged ≤ 63 years old but not in those aged > 63 years old. The results were shown in Table 4.

In the stratified analysis by gender. The rs6720283 A/A genotype showed a strong EC risk compared with the G/G genotype in male (OR = 1.78, 95% CI = 1.18 – 2.69, $p = 0.006$). We also observed that rs6720283 polymorphism presented an enhanced EC risk under the dominant model (OR = 1.43, 95% CI = 1.03 – 1.98, $p = 0.032$) the recessive model (OR = 1.51, 95% CI = 1.07 – 2.13, $p = 0.019$) and the Log- additive model (OR = 1.33, 95% CI = 1.09 – 1.64, $p = 0.006$) in males. No significant association between *CLO6A3* gene polymorphism and EC risk were found in females (Table 5).

Furthermore, when stratified analysis by alcohol drinking, our results confirmed that rs6720283 was significant increased the risk of EC in alcohol drinking group under the co-dominant model (OR = 2.13, 95% CI = 1.07 – 4.22, $p = 0.031$) and the Log-additive model (OR = 1.46, 95% CI = 1.03 – 2.05, $p = 0.031$). For the no alcohol drinking group, we observed that the A/A genotype of rs7436 was correlated with decreased the risk of EC under the co-dominant model (OR = 0.32, 95% CI = 0.12 – 0.89, $p = 0.029$) and the recessive model (OR = 0.33, 95% CI = 0.12 – 0.89, $p = 0.029$). Interestingly, the T/A and T/A – A/A genotypes of rs115510139 were interacted with enhanced EC risk in the no alcohol drinking group under the co-dominant model (OR = 2.02, 95% CI = 1.17 – 3.51, $p = 0.012$) and the dominant model (OR = 1.95, 95% CI = 1.17 – 3.25, $p = 0.010$). The results were listed in Table 6.

Subsequently, the stratification analysis was performed by BMI, the results suggested that rs115510139 T/A and T/A– A/A

**Table 6**
The association between the *COL6A3* gene polymorphisms and the risk of esophageal cancer stratified by alcohol drinking.

| SNP | Model | Genotype | Yes | | No | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | $P^a$ | OR (95% CI) | $P^a$ |
| rs1050785 | Co–dominant | G/G | 1 | | 1 | |
| | | G/T | 0.81 (0.45–1.45) | 0.473 | 1.58 (0.92–2.70) | 0.096 |
| | | T/T | 1.44 (0.72–2.89) | 0.305 | 1.84 (0.96–3.54) | 0.067 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/T – T/T | 0.98 (0.56–1.70) | 0.935 | 1.66 (1.00–2.75) | 0.051 |
| | Recessive | G/G – G/T | 1 | | 1 | |
| | | T/T | 1.66 (0.93–2.95) | 0.084 | 1.37 (0.78–2.39) | 0.271 |
| | Log–additive | – | 1.19 (0.85–1.67) | 0.311 | 1.37 (0.99–1.91) | 0.060 |
| rs7436 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 0.88 (0.52–1.48) | 0.629 | 0.96 (0.57–1.60) | 0.863 |
| | | A/A | 1.79 (0.19–16.47) | 0.608 | 0.32 (0.12–0.89) | 0.029* |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 0.91 (0.54–1.52) | 0.712 | 0.81 (0.50–1.30) | 0.378 |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 1.86 (0.20–17.03) | 0.583 | 0.33 (0.12–0.89) | 0.029* |
| | Log–additive | – | 0.95 (0.59–1.53) | 0.840 | 0.74 (0.50–1.09) | 0.122 |
| rs13032404 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 0.64 (0.38–1.08) | 0.092 | 1.15 (0.70–1.89) | 0.573 |
| | | A/A | 1.06 (0.47–2.37) | 0.892 | 1.83 (0.89–3.77) | 0.099 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 0.71 (0.43–1.17) | 0.175 | 1.29 (0.81–2.06) | 0.278 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.37 (0.65–2.88) | 0.408 | 1.70 (0.87–3.33) | 0.122 |
| | Log–additive | – | 0.90 (0.63–1.29) | 0.572 | 1.30 (0.93–1.81) | 0.120 |
| rs115510139 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 1.35 (0.76–2.41) | 0.302 | 2.02 (1.17–3.51) | 0.012* |
| | | A/A | 1.09 (0.57–2.07) | 0.802 | 1.83 (0.98–3.42) | 0.056 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 1.25 (0.73–2.12) | 0.413 | 1.95 (1.17–3.25) | 0.010* |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 0.90 (0.52–1.55) | 0.707 | 1.17 (0.69–1.97) | 0.560 |
| | Log–additive | – | 1.05 (0.75–1.45) | 0.785 | 1.37 (0.99–1.89) | 0.056 |
| rs2645765 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.21 (0.73–2.00) | 0.471 | 0.80 (0.49–1.30) | 0.371 |
| | | A/A | 0.86 (0.36–2.03) | 0.725 | 0.51 (0.23–1.16) | 0.107 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.14 (0.70–1.84) | 0.605 | 0.74 (0.47–1.17) | 0.196 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 0.79 (0.34–1.80) | 0.569 | 0.56 (0.26–1.24) | 0.153 |
| | Log–additive | – | 1.03 (0.71–1.50) | 0.879 | 0.75 (0.52–1.06) | 0.105 |
| rs6720283 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.40 (0.79–2.49) | 0.251 | 0.87 (0.51–1.49) | 0.612 |
| | | A/A | 2.13 (1.07–4.22) | 0.031* | 1.40 (0.70–2.80) | 0.341 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.61 (0.94–2.77) | 0.085 | 0.99 (0.59–1.66) | 0.970 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.70 (0.96–3.04) | 0.070* | 1.54 (0.85–2.77) | 0.152 |
| | Log–additive | – | 1.46 (1.03–2.05) | 0.031* | 1.15 (0.83–1.60) | 0.405 |

CI, confidence interval; OR, odds ratio; SNP: single nucleotide polymorphism.
*$p^a < 0.05$ indicates statistical significance.

genotypes were associated with enhanced EC risk in the BMI ≥ 24 group under the co-dominant model (OR = 2.31, 95% CI = 1.09 – 4.90, $p = 0.030$) and the dominant model (OR = 2.19, 95% CI = 1.07 – 4.47, $p = 0.032$), respectively. For rs6720283, the G/A – A/A genotype was increased the risk of EC in the BMI < 24 group under the dominant model (OR = 1.63, 95% CI = 1.02 – 2.60, $p = 0.042$). In addition, we also demonstrated that the A/A genotype of rs6720283 was correlated with increased the risk of EC in the BMI ≥ 24 group under the co-dominant model (OR = 2.42, 95% CI = 1.03 – 5.68, $p = 0.043$) and the recessive model (OR = 2.67, 95% CI = 1.32 – 5.42, $p = 0.007$), respectively. All results were shown in Table 7.

In accordance with the stratified analyses by TNM stage and lymph node metastasis. There was no statistical significant was found between the *COL6A3* gene polymorphisms and clinicopathological parameters such as TNM stage and lymph node metastasis among EC patients ($p > 0.05$). Supplementary Table 1 and 2 listed the results.

*Linkage disequilibrium and haplotype analysis of* COL6A3

Haplotype analyses of all SNPs were performed to examine the association between *COL6A3* haplotype and the risk of esophageal cancer in this study. Among the six SNPs, rs1050785 and rs7436 were in high Linkage disequilibrium (LD) (Fig. 1). Whereas, haplotype results were not observed to be associated with esophageal cancer risk (Supplementary Table 3).

## Discussion

Esophageal cancer is a malignant tumor, and has a high incidence rates in developing countries, especially in China [11]. Previous researches evidenced that genetic polymorphism and susceptibility were important to EC [7,3,14]. Thus, we performed a case-control study to explore the interaction between *COL6A3* gene polymorphism and EC risk. Our results confirmed that the *COL6A3* rs6720283 ($G > A$) was related with susceptibility to EC.

**Table 7**
The association between the *COL6A3* gene polymorphisms and the risk of esophageal cancer stratified by BMI.

| SNP | Model | Genotype | < 24 | | ≥ 24 | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | $P^a$ | OR (95% CI) | $P^a$ |
| rs1050785 | Co–dominant | G/G | 1 | | 1 | |
| | | G/T | 1.00 (0.59–1.70) | 0.996 | 1.06 (0.52–2.17) | 0.874 |
| | | T/T | 1.03 (0.57–1.88) | 0.919 | 1.10 (0.48–2.54) | 0.821 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/T – T/T | 1.01 (0.62–1.66) | 0.962 | 1.07 (0.55–2.11) | 0.839 |
| | Recessive | G/G – G/T | 1 | | 1 | |
| | | T/T | 1.03 (0.63–1.68) | 0.904 | 1.06 (0.54–2.10) | 0.869 |
| | Log–additive | – | 1.02 (0.75–1.37) | 0.918 | 1.05 (0.69–1.59) | 0.821 |
| rs7436 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 1.11 (0.69–1.80) | 0.661 | 0.58 (0.29–1.16) | 0.124 |
| | | A/A | 1.77 (0.37–8.37) | 0.474 | 0.76 (0.13–4.38) | 0.760 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 1.15 (0.72–1.84) | 0.553 | 0.60 (0.31–1.16) | 0.129 |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 1.71 (0.36–8.07) | 0.497 | 0.9 (0.16–5.12) | 0.908 |
| | Log–additive | – | 1.17 (0.77–1.78) | 0.464 | 0.67 (0.37–1.2) | 0.176 |
| rs13032404 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 0.68 (0.42–1.08) | 0.099 | 1.4 (0.73–2.66) | 0.311 |
| | | A/A | 1.19 (0.57–2.46) | 0.642 | 1.53 (0.64–3.69) | 0.341 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 0.76 (0.48–1.19) | 0.228 | 1.43 (0.78–2.62) | 0.249 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.49 (0.76–2.92) | 0.245 | 1.28 (0.57–2.85) | 0.550 |
| | Log–additive | – | 0.96 (0.7–1.31) | 0.792 | 1.27 (0.83–1.93) | 0.266 |
| rs115510139 | Co–dominant | T/T | 1 | | 1 | |
| | | T/A | 1.24 (0.74–2.09) | 0.422 | 2.31 (1.09–4.90) | 0.030* |
| | | A/A | 1.05 (0.58–1.90) | 0.872 | 1.98 (0.85–4.64) | 0.116 |
| | Dominant | T/T | 1 | | 1 | |
| | | T/A– A/A | 1.17 (0.72–1.90) | 0.528 | 2.19 (1.07–4.47) | 0.032* |
| | Recessive | T/T – T/A | 1 | | 1 | |
| | | A/A | 0.92 (0.56–1.50) | 0.726 | 1.13 (0.58–2.20) | 0.714 |
| | Log–additive | – | 1.03 (0.76–1.39) | 0.862 | 1.38 (0.92–2.08) | 0.122 |
| rs2645765 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 0.97 (0.62–1.53) | 0.908 | 1.03 (0.56–1.92) | 0.915 |
| | | A/A | 0.83 (0.38–1.84) | 0.652 | 0.94 (0.33–2.65) | 0.908 |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 0.95 (0.62–1.46) | 0.812 | 1.02 (0.56–1.83) | 0.959 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 0.84 (0.39–1.81) | 0.663 | 0.93 (0.34–2.51) | 0.881 |
| | Log–additive | – | 0.94 (0.67–1.31) | 0.708 | 0.99 (0.64–1.55) | 0.978 |
| rs6720283 | Co–dominant | G/G | 1 | | 1 | |
| | | G/A | 1.63 (0.99–2.71) | 0.056 | 0.86 (0.42–1.78) | 0.685 |
| | | A/A | 1.61 (0.89–2.90) | 0.114 | 2.42 (1.03–5.68) | 0.043* |
| | Dominant | G/G | 1 | | 1 | |
| | | G/A – A/A | 1.63 (1.02–2.60) | 0.042* | 1.18 (0.6–2.32) | 0.634 |
| | Recessive | G/G – G/A | 1 | | 1 | |
| | | A/A | 1.18 (0.71–1.96) | 0.519 | 2.67 (1.32–5.42) | 0.007* |
| | Log–additive | – | 1.29 (0.95–1.74) | 0.102 | 1.54 (1.00–2.39) | 0.052 |

CI, confidence interval; OR, odds ratio; SNP: single nucleotide polymorphism.
*$p^a < 0.05$ indicates statistical significance.

Type VI collagen (COL6) is a heterotrimer comprising three collagen chains, including the $\alpha$1 (VI), $\alpha$2 (VI) and $\alpha$3 (VI) collagen chains. *COL6* is an important of extracellular matrix component of most cartilage and soft tissues [17]. Accumulating researches confirmed that *COL6* was associated with varieties of diseases [18,19]. *COL6A3*, a member of *COL6* family, which is located in chromosome 2q37 and encodes collagen type VI alpha 3 chain [20]. Mutations of *COL6A3* gene has recently been suggest to be causative for neoplasms and Bethlem myopathy, a childhood onset muscular dystrophy with joint contractures [16,21]. Lee et.al studies suggested that the levels of *COL6A3* and its product, endotrophin (ETP) in tumor-neighboring regions are associated with poor prognosis in hepatocellular carcinoma (HCC) patients [22]. Liu et.al demonstrated that *COL6A3* knockout studies indicated the clinical relationship of *COL6A3* in the process of colorectal cancer (CRC) [23]. Dickson also found that *COL6A3* was associated with breast cancer [24]. However, to our knowledge, this is the first time to investigate the interaction between *COL6A3* variants and EC risk. Our results demonstrated that *COL6A3* rs6720283 was significantly increased the risk of EC under three genetic models, including the Log- additive, the dominant and the recessives models ($p = 0.002$, $p = 0.027$ and $p = 0.004$, respectively).

The mechanisms and Pathogenesis of esophagus cancer are very complicated; Recent studies have revealed that the causes of esophagus cancer mainly include environmental factors, such as smoking, dietary habit, drinking and genetic factors [25]. Yang e.al has shown that the genotypes C/C and R/C + C/C of *LMP2–60* gene were correlated with an increased EC risk in Kazakh patients aged > 57 years [4]. We also performed the stratified analysis by gender, age, alcohol drinking, BMI, TNM stage and lymph node metastasis status, the increased risk were observed in males patients aged ≤ 63 years old, alcohol drinking group and BMI≥ 24 group in our study. Interestingly, we also observed that rs115510139 was associated with increased EC risk in no alcohol drinking group. The detail molecular mechanism was necessary to be explore in our future researches. In addition, no statistical significant was found

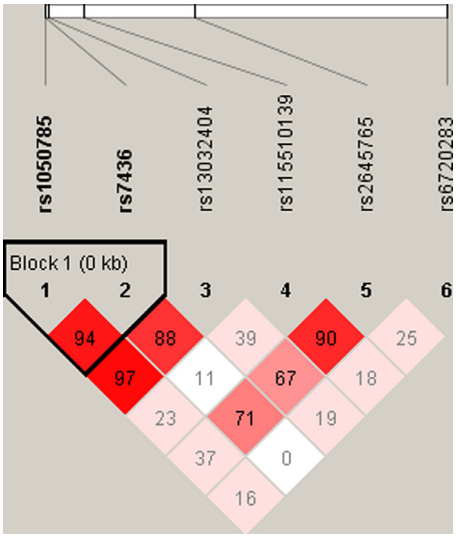


**Fig. 1.** Linkage disequilibrium patterns for six *COL6A3* SNPs.

between the *COL6A3* gene polymorphisms and TNM stage and lymph node metastasis among EC patients ($p > 0.05$) in our study.

Despite the adequate statistical power of the present study, several limitations were necessary to be considered. First, some clinical factors were missing, due to the hospital design. Next, we further increased the collection of information. Second, we first confirmed the *COL6A3* gene polymorphism and EC risk. However, the molecular mechanisms researches should be performed for our further study.

In conclusion, this case-control study suggested that the *COL6A3* rs6720283 ($G > A$) might affect personal susceptibility to EC. Our result provides a solid theoretical foundation for future research to investigate whether the existence of *COL6A3* genetic variants could be useful for EC diagnosis.

## Acknowledgement

We are grateful to all participants for providing blood samples. We also appreciate the reviewers and editors for their efforts and patience.

## Conflict of interest

The authors have declared that they have no conflict of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.07.003.

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