XAB2 TagSNP is Associated with the Risk of Gastric Cancer in Chinese Population: a case-control study

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Abstract

Background: XAB2 protein (xeroderma pigmentosum group A-binding protein 2) plays a significant role in the nucleotide excision repair pathway and transcription coupled DNA repair. Polymorphisms in XAB2 gene may effect on the capability of DNA repair and further contribute to the risk of developing various cancers. Methods: in order to investigate the relationship between XAB2 genetic variants and the risk of gastric cancer, we performed a hospital-based case-control study. XAB2 tagSNPs were genotyped by using iPlex Gold Genotyping Asssy and Sequenom MassArray. By conducting logistic regression, odds ratio (OR) and 95% confidence interval (CI) were used to represent the association of XAB2 tagSNPs with the risk of gastric cancer. Results: Our results showed that XAB2 rs794078 AA genotype was associated with a significantly lower risk of gastric cancer compared with GG genotype with OR (95%CI) of 0.33(0.12-0.91). Stratified analysis indicated a significantly decreased risk for gastric cancer among smokers with rs794078 AA genotype compared with non-smokers with GG genotype (OR=0.11, 95%CI=0.01-0.91, P=0.040). The gene-gene interactions by multifactor dimensionality reduction (MDR) showed that tagSNP rs794078 was the best predictive elements for gastric cancers (Testing Bal. Acc=51.68%, P=0.055, cross-validation consistency=9). Conclusion: The XAB2 tagSNP rs794078 were significantly associated with the risk of gastric cancer in Chinese population, which proved the important role of XAB2 in the development of gastric cancer.

Background

Gastric cancer is the fourth most common cancer and the third cancer death in China[1]. Although the incidence of gastric cancer has reduced rapidly year by year, it is still one of the major cancer types[2]. Many environmental factors contributed to the occurrence of gastric cancer, such as dietary habit, tobacco smoking, antioxidant using and bacterial
infection[3]. Despite acquired factors can cause gastric cancer, genetic susceptibility is also considered to be some extent primary reason for individual difference of gastric cancer[4, 5]. DNA repair system provides cellular responses to DNA damage in living cells, protects the genome from carcinogenic damage and plays a pivotal role in the maintenance of genomic stability. Severe damaged DNA repair capacity could lead to DNA mutation and further cause many types of cancer, such as squamous cell carcinoma of head and neck, breast carcinoma and gastric cancer[6-8]. DNA repair system contains more than 130 genes which is mainly divided into four repair pathways: nucleotide excision repair (NER), mismatch repair (MMR), base excision repair (BER) and double-strand break repair (DSBR)[9, 10]. By removing a large amount of regional chromosome DNA damage through “cut-patch” mechanism, NER helps DNA resisting the negative impact of mutation[11, 12]. NER contains two types of repair mechanism, transcription-coupled repair (TCR) and global genome repair (GGR). TCR rapidly removes lesions during transcription and GGR restores the rest of genome slower[13]. Polymorphisms in NER key components could reduce DNA repair capacity and contribute to the development of various of cancers. For example, ERCC1 rs11615 and ERCC5 rs17655 polymorphisms were associated with increased risk of laryngeal cancer[14] and XPD Lys751Gln was associated with the increased risk of digestive tract cancer[15]. XAB2 involved in the process of both global genome and transcription coupled repair by interacting with XPA[16]. XAB2 also interacted with Cockayne syndrome groups A (CSA), Cockayne syndrome groups B (CSB), as well as RNA polymerase II to initial the DNA repair after DNA damage[17]. XAB2 was also involved in pre-mRNA splicing, leading to preimplantation lethality in vitro and in vivo studies[18]. The down-regulation of XAB2 could result in RNA synthesis interference and the decrease of mRNA splicing efficiency[19]. All of these suggested that XAB2 was an important NER component. Polymorphisms in XAB2 may lead to altered nucleotide excision
repair function and contribute to the occurrence of cancer. In order to investigate the role of XAB2 genetic variations in the development of gastric cancer, tagSNPs of XAB2 were selected and surveyed in a hospitals-based case-control study in Chinese population.

**Methods**

**Study population**

In this hospital-based case-control study, 500 patients with gastric cancer and 500 cancer-free controls were included. Both patients and healthy controls were all Han Chinese residents which recruited at Affiliated Tangshan Gongren Hospital of North China University of Science and Technology (Tangshan, China) between January 2008 and April 2013. All of controls were matched with cases on age (±5 years) and sex. We defined the eligible cancer-free controls as subjects who had no individual history of cancer and digestive disease, while cases were subjects newly diagnosed gastric cancer. People with other malignancies were also excluded from this study. Our study was approved by the institutional review board from the Human Ethics Review Committee of North China University of Science and Technology. The detailed information about volunteers’ gender, age, and smoking status were also collected after obtaining the informed consent of each subject.

**TagSNPs selection and genotype**

To select tag SNPs of XAB2, the HapMap database (HapMap Data Rel27/Phasell+III, on NCBI B36 assembly, dbSNP b126) was discovered. The selection criteria included that $\gamma^2 \geq 0.8$ for all SNPs with a minor allele frequency (MAF) $\geq 0.05$ based on pairwise linkage disequilibrium (LD) information. Genomic DNA of all participants was extracted and purified from the peripheral blood lymphocytes and ethanol precipitation within 1 week after using proteinase K digestion. All genotyping was performed with iPlex Gold
Genotyping Assay and Sequenom MassArray (Sequenom, San Diego, CA, USA) at BomiaoTech (Beijing, China). PCR and extension primers for each SNP were designed by Sequenom's MassArray Designer.

**Statistical analysis**

The differences of demographic variables, smoking status, and the distribution of genotypes between gastric cancer and controls were estimated by two-side chi-square test separately. Hard-Weinberg equilibrium of the control genotype distribution was tested by goodness-of-fit chi-square test. We performed multivariate logistic regression models after matching a hospital-based case-control study, odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the strength of the association between genotypes and risk of gastric cancer. The non-parametric multifactor dimensionality reduction (MDR) was employed to investigate gene-gene interaction[20]. Testing accuracy higher than 50% indicated a meaningful result. The cross-validation consistency (CVC) presents the number of times a particular combination of factors identified in the same best model. All tests were performed with SPSS software package (version 23.0; IBM, NY, USA), and P<0.05 was used as the criterion of significant differences in all statistical analysis.

**Results**

**Baseline characteristics of study population**

The basic information of 500 cases and 500 controls were summarized in Table1. There are 74.4% males and 28.6% females among cases, and 68.8% males and 31.2% females among controls. There were no statistically significant differences in the distributions of gender between cases and controls (P=0.407). 58.8% and 60.4% of cases and controls were non-smoker, while 41.2% and 39.6% were smoker (P=0.652), there was also no significant difference in the distribution of smoking status among cases and controls.
**Selected SNPs and the risk of gastric cancer**

Using HaploView program, five tag SNPs (rs4134860 T>C, rs794078 G>A, rs794083 C>G, rs4134816 T>C, rs4134819 A>G) were selected for further study. All of selected tag SNPs were intron variant except for rs794078, which was located in exon. The genotype frequency of the controls was in agreement with the Hardy-Weinberg equilibrium (P>0.05). The observed genotype frequencies in participants and the association of genotypes with gastric cancer were presented in Table 2. Of all selected SNPs in XAB2 genes, only one SNP was identified to be associated with the risk of gastric cancer between cases and controls. For XAB2 rs794078 G>A polymorphism, we found that AA genotype carriers had a significantly decreased risk for developing gastric cancer (OR= 0.33; 95% CI= 0.12-0.91) in comparison to those with GG genotype. The rs794078 heterozygous AG is not associated with the risk of gastric cancer with OR (95%CI) of 1.29 (0.95-1.76). We did not find that any other selected SNPs were associated with the risk of gastric cancer.

Multifactor dimensionality reduction (MDR) was used to further investigate gene-gene interaction and shown in Table 3. The rs794078, rs794083, rs4134819 interaction model indicated high testing balance accuracy but was still lower than rs794078, rs4134819 interaction model. The representative interaction model was rs794078, which was the best predictive factor for gastric cancer (Testing Bal. Acc=51.68%, P=0.055, cross-validation consistency=9).

**XAB2 rs794078 variant and gastric cancer by smoking**

To evaluate the effect of environmental factors on the association of XAB2 polymorphisms with the risk of gastric cancer, an unconditional multivariate logistic regression model was used, our data showed that the smokers with XAB2 rs794078 AA genotypes had a significantly decreased risk of gastric cancer compared to non-smokers with common GG
genotype (OR=0.11, CI=0.11-0.91, P=0.040), suggesting rs794078 AA genotype was a protective factor for gastric cancer in smokers (Table 4). We did not find that rs794078 variant effected on the risk of gastric cancer when stratified by smoking status.

Discussion

As an important component of DNA repair pathway, XPA protein is a kind of conservative DNA repair enzyme. It involves in excision the genome harmful mutations and prevention of cancer. XAB2 was defined as XPA-interacting protein, which consists of 15 tetratricopeptide repeats with 855 amino acids, it has been purified by means of combination with XPA in the yeast two-hybrid system[19]. XAB2 inhibited all-trans retinoic acid (ATRA)-induced cellular differentiation by interacting with the transcriptional repressor complex existing in retinoic acid response elements (RARE)[21]. It involved in DNA repair pathway in the form of XAB2 complex, which included subunits such as hAquarius, hPRP19, XAB2, CCDC16, hISY1, and PPIE[16]. A large number of studies have confirmed that XAB2 plays a crucial role in the NER pathway, TCR and transcription itself[18, 22], the relationship between genetic polymorphisms of XAB2 and cancer was rarely reported. DNA mutations, gene-environment interactions have close relationship with gastric carcinogenesis[20]. Many researches indicated tagSNPs were associated with gastric cancer. For instance, decay-accelerating factor (DAF) rs10746463 AA genotype was associated with the increased risk of gastric cancer compared in Chinese population[23]. Polymorphisms of NER pathway components were also associated with the risk of gastric cancer and other cancers, but the effects were not consistent. For instance, ERCC5 rs1047768 variant reduced the risk of gastric cancer[24], ERCC3 rs4150403 was associated with increased susceptibility for head and neck cancer in whites, and ERCC6 rs4253132 polymorphism decreased the risk of head and neck cancer among African Americans[24]. In the present study, we found that XAB2 tagSNP rs794078 AA genotype
was associated with decreased risk of gastric cancer in Chinese population. This result proved the important role of DNA repair gene in the development of gastric cancer. Cigarette contains carcinogens such as 4-aminobiphenyl and nitric oxide, which could cause DNA damage and cancer[25]. Cigarette smoking, nicotine and nicotine-derived nitrosamine could lead to gastrointestinal cancer[25]. Recent research has shown that smoking was considered to be the major causal factor of gastric cancer[26]. Several researches demonstrated the interaction of SNPs with smoking status in the development of certain cancer, but the effects were not consistent. For instance, smokers with decay-accelerating factor rs10746463 A allele containing genotype have increased risk of gastric cancer[26]. Tumor necrosis factor TNF-α-1031 T/C, TNF-α-863 C/A and TNF-α-857 C/T were also associated with higher risk for gastric cancer among smokers[27]. In our study, smokers with rs794078 G>A variant was associated with a significantly decreased risk of gastric cancer. This finding demonstrated a reverse association between XAB2 rs794078 and gastric cancer risk in Chinese population. This result was in accordance with the study of the CYP1A1 polymorphism, which showed that smokers with T6235C transition polymorphism have a significantly lower risk of developing gastric cancer[28].

Conclusions

In conclusion, our results showed that XAB2 rs794078 was associated with the decreased risk of gastric cancer. However, there were several limitations in our study because of the selection bias and small sample size. In the future, large study still needs to be done and the molecular biological mechanism need to be discovered.

Abbreviations

XAB2: xeroderma pigmentosum group A-binding protein 2; NER: nucleotide excision repair;
MMR: mismatch repair; BER: base excision repair; DSBR: double-strand break repair; TCR: transcription-coupled repair; GGR: global genome repair; CSA: cockayne syndrome groups A; CSB: cockayne syndrome groups B

Declarations

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Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

YX and YY: acquisition, analysis, and interpretation of data; drafting the manuscript. HW and HG: data collection and analysis. ZY, YZ, HW, HF: DNA extraction; acquisition and interpretation of data. XZ: design of the work, analysis and interpretation of data, revision of the article, final approval of the version to be published. All authors read and approved the final manuscript.
Ethics approval and consent to participate

All the study procedures were approved by the Ethics Committee of North China University of Science and Technology (12-002) and written informed consents were obtained from all participants of their own free will.

Consent for publication

Not applicable.

Conflict of Interest

The authors declare that they have no competing interests.

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Tables

**Table 1** Distributions of select characteristics in cases and control subjects.

| Variables      | Cases (n=500) | Controls (n=500) | P value |
|----------------|---------------|------------------|---------|
|                | No ( %)       | No ( %)          |         |
| Sex            |               |                  |         |
| Male           | 357 (71.4)    | 344 (68.8)       | 0.407   |
| Female         | 143 (28.6)    | 156 (31.2)       |         |
| Age            |               |                  | 0.317   |
| ≤50            | 141 (28.2)    | 156 (31.2)       |         |
| 51-60          | 149 (29.8)    | 157 (31.4)       |         |
| >60            | 210 (42.0)    | 187 (37.4)       |         |
| Smoking status |               |                  | 0.652   |
| Non-smoker     | 294 (58.8)    | 302 (60.4)       |         |
| Smoker         | 206 (41.2)    | 198 (39.6)       |         |

**Table 2** Genotype frequencies of XAB2 among cases and controls and their association with gastric cancers.
| Genotypes | Controls (n=500) | Cases (n=500) | OR (95% CI) | P value |
|-----------|-----------------|--------------|-------------|---------|
|           | No (%)          | No (%)       |             |         |
| rs4134860 |                 |              |             |         |
| TT        | 363 (72.6)      | 350 (70.0)   | 1.10(0.83-1.46) | 0.510   |
| CT        | 127 (25.4)      | 136 (27.2)   | 1.10(0.64-3.37) | 0.367   |
| CC        | 10 (2.0)        | 14 (2.8)     |             |         |
| rs794078  |                 |              |             |         |
| GG        | 392 (78.4)      | 378 (75.6)   |             |         |
| AG        | 93 (18.6)       | 117 (23.4)   | 1.29(0.71-1.76) | 0.105   |
| AA        | 15 (3.0)        | 5 (1.0)      | 0.33(0.12-0.91) | 0.032   |
| rs794083  |                 |              |             |         |
| CC        | 241 (48.2)      | 237 (47.4)   |             |         |
| CG        | 199 (39.8)      | 209 (41.8)   | 1.07(0.22-1.39) | 0.638   |
| GG        | 60 (12.0)       | 54 (10.8)    | 0.93(0.61-1.40) | 0.710   |
| rs4134816 |                 |              |             |         |
| TT        | 461 (92.2)      | 470 (94.0)   |             |         |
| CT        | 39 (7.8)        | 30 (6.0)     | 0.81(0.49-1.34) | 0.411   |
| rs4134819 |                 |              |             |         |
| AA        | 129 (25.8)      | 112 (22.4)   |             |         |
| AG        | 246 (49.2)      | 253 (50.6)   | 1.18(0.87-1.62) | 0.287   |
| GG        | 125 (25.0)      | 135 (27.0)   | 1.26(0.89-1.80) | 0.199   |

Table 3 Summary of MDR gene-gene interaction results for XAB2 gene.

| Models | Training Bal. Acc (%) | Testing Bal. Acc. (%) | P value | Cross-validation Consistency |
|--------|-----------------------|-----------------------|---------|-----------------------------|
| rs794078 | 52.40 | 51.68 | 0.055 | 9/10 |
| rs794078, rs4134819 | 53.38 | 50.22 | 0.623 | 8/10 |
| rs794078, rs794083, rs4134819 | 54.29 | 50.01 | 0.623 | 4/10 |

Table 4 Risk of XAB2 rs794078 genotypes with gastric cancer by smoking status.
| Genotype | Nonsmoker | OR (95%CI) | P value | Smoker | OR (95%CI) | P value |
|----------|-----------|------------|---------|--------|------------|---------|
| GG       | 229/243   | 1.00       |         | 149/149| 1.02 (0.74-1.42) | 0.891   |
| AG       | 61/53     | 1.21 (0.81-1.83) | 0.354   | 56/40  | 1.47 (0.92-2.34) | 0.107   |
| AA       | 4/6       | 0.69 (0.19-2.48) | 0.567   | 1/9    | 0.11 (0.01-0.91) | 0.040   |

Number of cases/number of controls.

§ Data were calculated by logistic regression and adjusted for age and gender.