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

Yuning Xie
North China University of Science and Technology
Yuan Yu
North China University of Science and Technology
Hongjiao Wu
North China University of Science and Technology
Hui Gao
North China University of Science and Technology
Zhengbang Yang
North China University of Science and Technology
Yi Zhang
North China University of Science and Technology
Xuemei Zhang (jyxuemei@gmail.com)
North China University of Science and Technology https://orcid.org/0000-0003-0705-4231

Research article

Keywords: XAB2, Gastric cancer, polymorphism, TagSNPs, DNA repair

Posted Date: September 24th, 2019

DOI: https://doi.org/10.21203/rs.2.14847/v1

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/PhaseII+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) ≥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 tagSNPs 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. 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

Acknowledgments

The authors thank all patients and control subjects for their participation.

Funding

This work was supported by Key Project of Natural Science Foundation of Hebei province of China (H2017209233 to X. Zhang), Leader talent cultivation plan of innovation team in Tangshan city (14130225B to X. Zhang), Leader talent cultivation plan of innovation team in Hebei province (LJRC001 to X. Zhang) and National Natural Science Foundation of China (81101483 to X. Zhang).

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.

Author details

[1]College of Life Science, North China University of Science and Technology, Tangshan, 063210, China.[2]School of Public Health, North China University of Science and Technology, Tangshan, 063210, China.[3]School of Basic Medical Sciences, North China University of Science and Technology, Tangshan, 063210, China.

References

1. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, Yang Z, Li H, Zou X, He J: **Cancer incidence and mortality in China, 2014**. *Chinese journal of cancer research = Chung-kuo yen cheng yen chiu* 2018, **30**(1):1-12.
2. Jemal A, Center MM, DeSantis C, Ward EM: **Global patterns of cancer incidence and mortality rates and trends**. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2010, **19**(8):1893-1907.

3. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F: **Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention**. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2014, **23**(5):700-713.
4. Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F: **Familial gastric cancer: genetic susceptibility, pathology, and implications for management**. *The Lancet Oncology* 2015, **16**(2):e60-70.
5. Mocellin S, Verdi D, Pooley KA, Nitti D: **Genetic variation and gastric cancer risk: a field synopsis and meta-analysis**. *Gut* 2015, **64**(8):1209-1219.
6. Decordier I, Loock KV, Kirsch-Volders M: **Phenotyping for DNA repair capacity**. *Mutation research* 2010, **705**(2):107-129.
7. Ramos JM, Ruiz A, Colen R, Lopez ID, Grossman L, Matta JL: **DNA repair and breast carcinoma susceptibility in women**. *Cancer* 2004, **100**(7):1352-1357.
8. Marteijn JA, Lans H, Vermeulen W, Hoeijmakers JH: **Understanding nucleotide excision repair and its roles in cancer and ageing**. *Nat Rev Mol Cell Biol* 2014, **15**(7):465-481.
9. Hoeijmakers JH: **Genome maintenance mechanisms for preventing cancer**. *Nature* 2001, **411**(6835):366-374.
10. Iyama T, Wilson DM, 3rd: **DNA repair mechanisms in dividing and non-dividing cells**. *DNA Repair (Amst)* 2013, **12**(8):620-636.
11. Godon C, Mourgues S, Nonnekens J, Mourcet A, Coin F, Vermeulen W, Mari PO, Giglia-Mari G: **Generation of DNA single-strand displacement by compromised nucleotide excision repair**. *The EMBO journal* 2012, **31**(17):3550-3563.
12. Gong Y, He C, Duan Z, Sun L, Xu Q, Xing C, Yuan Y: **Association of two ERCC4 tagSNPs with susceptibility to atrophic gastritis and gastric cancer in Chinese**. *Gene* 2013, **519**(2):335-342.
13. Butkiewicz D, Rusin M, Enewold L, Shields PG, Chorazy M, Harris CC: **Genetic polymorphisms in DNA repair genes and risk of lung cancer**. *Carcinogenesis* 2001, **22**(4):593-597.
14. Lu B, Li J, Gao Q, Yu W, Yang Q, Li X: **Laryngeal cancer risk and common single nucleotide polymorphisms in nucleotide excision repair pathway genes ERCC1, ERCC2, ERCC3, ERCC4, ERCC5 and XPA**. *Gene* 2014, **542**(1):64-68.
15. Du H, Guo N, Shi B, Zhang Q, Chen Z, Lu K, Shu Y, Chen T, Zhu L: **The effect of XPD polymorphisms on digestive tract cancers risk: a meta-analysis**. *PloS one* 2014, **9**(5):e96301.
16. Kuraoka I, Ito S, Wada T, Hayashida M, Lee L, Saijo M, Nakatsu Y, Matsumoto M, Matsunaga T, Handa H *et al*: **Isolation of XAB2 complex involved in pre-mRNA splicing, transcription, and transcription-coupled repair**. *The Journal of biological chemistry* 2008, **283**(2):940-950.
17. Nakatsu Y, Asahina H, Citterio E, Rademakers S, Vermeulen W, Kamiuchi S, Yeo JP, Khaw MC, Saijo M, Kodo N *et al*: **XAB2, a novel tetratricopeptide repeat protein involved in transcription-coupled DNA repair and transcription**. *The Journal of biological chemistry* 2000, **275**(45):34931-34937.

18. Yonemasu R, Minami M, Nakatsu Y, Takeuchi M, Kuraoka I, Matsuda Y, Higashi Y, Kondoh H, Tanaka K: **Disruption of mouse XAB2 gene involved in pre-mRNA splicing, transcription and transcription-coupled DNA repair results in preimplantation lethality**. *DNA Repair (Amst)* 2005, **4**(4):479-491.
19. Fousteri M, Mullenders LH: **Transcription-coupled nucleotide excision repair in mammalian cells: molecular mechanisms and biological effects**. *Cell Res* 2008, **18**(1):73-84.
20. Ritchie MD, Hahn LW, Moore JH: **Power of multifactor dimensionality reduction for detecting gene-gene interactions in the presence of genotyping error, missing data, phenocopy, and genetic heterogeneity**. *Genetic epidemiology* 2003, **24**(2):150-157.
21. Ohnuma-Ishikawa K, Morio T, Yamada T, Sugawara Y, Ono M, Nagasawa M, Yasuda A, Morimoto C, Ohnuma K, Dang NH *et al*: **Knockdown of XAB2 enhances all-trans retinoic acid-induced cellular differentiation in all-trans retinoic acid-sensitive and -resistant cancer cells**. *Cancer research* 2007, **67**(3):1019-1029.
22. Fousteri M, Vermeulen W, van Zeeland AA, Mullenders LH: **Cockayne syndrome A and B proteins differentially regulate recruitment of chromatin remodeling and repair factors to stalled RNA polymerase II in vivo**. *Molecular cell* 2006, **23**(4):471-482.
23. Song Q, Zhang Z, Liu Y, Han S, Zhang X: **The tag SNP rs10746463 in decay-accelerating factor is associated with the susceptibility to gastric cancer**. *Molecular immunology* 2015, **63**(2):473-478.
24. Hussain SK, Mu LN, Cai L, Chang SC, Park SL, Oh SS, Wang Y, Goldstein BY, Ding BG, Jiang Q *et al*: **Genetic variation in immune regulation and DNA repair pathways and stomach cancer in China**. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2009, **18**(8):2304-2309.
25. Moinuddin, Dixit K, Ahmad S, Shahab U, Habib S, Naim M, Alam K, Ali A: **Human DNA damage by the synergistic action of 4-aminobiphenyl and nitric oxide: an immunochemical study**. *Environmental toxicology* 2014, **29**(5):568-576.
26. Tramacere I, La Vecchia C, Negri E: **Tobacco smoking and esophageal and gastric cardia adenocarcinoma: a meta-analysis**. *Epidemiology (Cambridge, Mass)* 2011, **22**(3):344-349.
27. Yang JJ, Ko KP, Cho LY, Shin A, Gwack J, Chang SH, Shin HR, Yoo KY, Kang D, Park SK: **The role of TNF genetic variants and the interaction with cigarette smoking for gastric cancer risk: a nested case-control study**. *BMC cancer* 2009, **9**:238.
28. Han F, Wang X, Wang X, Luo Y, Li W: **Meta-analysis of the association of CYP1A1 polymorphisms with gastric cancer susceptibility and interaction with tobacco smoking**. *Molecular biology reports* 2012, **39**(8):8335-8344.

Tables

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

Variables	Cases (n=500)		Controls (n=500)		P value
	No	(%)	No	(%)	
Sex					0.407
Male	357	71.4	344	68.8	
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		
CT	127	25.4	136	27.2	1.10(0.83-1.46)	0.510
CC	10	2.0	14	2.8	1.47(0.64-3.37)	0.367
rs794078						
GG	392	78.4	378	75.6		
AG	93	18.6	117	23.4	1.29(0.95-1.76)	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(0.82-1.39)	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	Smoking status					
	Nonsmoker	OR (95%CI)§	*P* value	Smoker	OR (95%CI)§	*P* value
GG	229/243	1.00 (reference)		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.