Oncology Treatment Discovery, 2024, Volume 2, Issue 1
http://ojs.bbwpublisher.com/index.php/OTD

Study on the Association of XRCC1 Gene rs72484243 Polymorphisms with Increased Laryngeal Cancer Risk

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Abstract: *Objective:* To study the association of X-ray repair cross-complementing group 1 (XRCC1) gene polymorphisms with increased laryngeal cancer risk. *Methods:* A total of 120 individuals, comprising 60 patients with laryngeal squamous cell carcinoma (LSCC), and 60 healthy volunteers participated were selected. Blood samples were taken and analyzed, and 4 XRCC1 polymorphisms (rs145135970, rs1799780, rs25489, and rs72484243) were genotyped. *Results:* Gender, age, body mass index (BMI), and smoking habits were shown to be the high-risk factors for LSCC. Genotype and allele distributions for the 4 polymorphisms differed significantly between both groups ($P < 0.05$). Furthermore, carriers with the rs72484243GTGT- allele exhibited an increased risk of LSCC relative to those who had the rs145135970 GTGTGTGTGTGTGT- allele, the rs1799780 G-A allele, or the rs25489 C-T allele, as determined by binary logistic regression analysis ($OR = 2.74$, 95% CI: 1.27–5.91, $P = 0.01$), after accounting for possible co-factors like sex, age, BMI, drinking and smoking behavior, and special diet requirements. In addition, a TA haplotype and a GTGTGTGTGTGTTG haplotype were linked to LSCC in Chinese populations in a haploid association study of 4 SNP loci in the XRCC1 gene ($P = 0.05$ $OR = 1.36$, 95% CI = 1.1228–1.6406). *Conclusion:* Genetic polymorphisms of the XRCC1 gene at the rs72484243 site were correlated with an elevated risk of LSCC among the Xinjiang population.

Keywords: XRCC1 gene; Single nucleotide polymorphism; Susceptibility gene; Laryngeal cancer

Online publication: March 29, 2024

1. Introduction

Head and neck squamous cell carcinomas (HNSCCs) is the sixth most prevalent types of malignancy worldwide and represent a heterogeneous group of malignancies that arise from the mucosal epithelium of the oral cavity, pharynx, nasal cavity, paranasal sinuses, and larynx [1,2]. Laryngeal squamous cell carcinoma (LSCC) accounts for one-third of all HNSCC cases and ranks second in terms of prevalence among cancers [3]. The incidence and mortality of laryngeal cancer worldwide were up to 2.76 cases/year per 100,000 population and 1.66 deaths/year per 100,000 population, respectively [4]. Men are predisposed to a greater risk of developing LSCC (5.8 cases per 100,000 for men vs 1.2 per 100,000 for women) [2].

The incidence varies considerably across different populations and ethnic groups [3,5,6]. This indicates that the risk of LSCC is influenced by various environmental and lifestyle factors. The human papillomavirus (HPV) and the Epstein-Barr virus (EBV) as well as occupational exposure to carcinogens are the most common causes of LSCC [6,7]. Due to the challenges in early diagnosis, three out of every five patients are already in an advanced state (stages III or IV) upon diagnosis [7]. Despite the overall decline in incidence over the last 4 decades, the 5-year survival rate has only dropped from 66% to 63%. Research should prioritize developing better methods of early detection as a means of increasing both the patient's survival rate and quality of life.

Laryngeal cancer has a complex etiology that includes exposure to common carcinogens, genetic polymorphism, HPV infection, immune suppression, laryngopharyngeal reflux, and occupational factors [8–10]. DNA damage could be induced by the aforementioned carcinogens, which may then trigger apoptosis or uncontrolled cell proliferation, eventually leading to cancer. Hence, DNA repair genes are crucial to ensure genomic integrity. This indicates that mutations in DNA-repair genes may contribute to the onset and progression of LSCC [11]. Studies showed that polymorphisms of GLUT1, HIF1α, and TBX21 genes had no association with laryngeal cancer development [12]. The telomerase reverse transcriptase gene TERT-CLPTM1L, plays a key role in the formation and progression of various cancers. Yu *et al*. reported that this gene may be a significant biomarker for the susceptibility to oropharyngeal and laryngeal cancers [13]. A study was carried out on the association between CD14 gene polymorphism and risk of laryngeal cancer [14]. Ekizoglu *et al*. indicated that the gene SLC22A23 (solute carrier family 22, member 23) may play a significant role in the risk of laryngeal cancer [15]. A recent study also showed that rs6620138DIAPH2 polymorphism could increase the onset risk of laryngeal cancer [16].

X-ray repair cross-complementing group 1 (XRCC1) is a gene that protects DNA against harmful carcinogens by participating in the base excision repair (BER) pathway. The XRCC1 protein is essential in the process of repairing single-stranded DNA fractures [11–17]. The protection is achieved based on the genes that are involved in DNA repair pathways and the maintenance of genomic stability [18–20]. Research has shown that various polymorphisms in DNA repair genes were linked to different pathologies, including lung cancer, polycystic ovary syndrome (PCOS), ovarian cancer, breast cancer, and myeloid leukemia [19,21–25]. Polymorphisms in DNA repair genes could influence the functioning of the protein products of those genes [19].

The three most crucial DNA repair pathways are BER, double-strand break (DSB) repair, and nucleotide excision repair (NER) [3]. The development of cancer begins with mutations and some studies suggested that impaired DNA repair was associated with a higher chance of developing several cancers [5–17]. Nonetheless, the XRCC1 gene's possible link to LSCC has only been the subject of a few studies [26]. Therefore, this study analyzes the association between polymorphisms in the XRCC1 gene and the risk of LSCC in a population from northwest China.

2. Methods

2.1. Ethical statement

This research was approved by the First Affiliated Hospital of Xinjiang Medical University ethics committee and it was conducted following the principles stipulated in the Helsinki Declaration. All participants or their legal guardians provided informed consent.

2.2. Subjects and clinical parameters

One hundred and twenty LSCC patients admitted between January 2021 to October 2023 were selected and divided into two groups, 60 patients with LSCC and 60 healthy individuals. The information on patients and control baseline characteristics (gender, age, drinking behavior, smoking status, and special diet requirements) was gathered via in-person interviews, health record searches, and pathology reports.

2.3. Blood sample preparation and DNA isolation

The patients were instructed to fast for more than 12 hours and blood was drawn from their cubital veins. Materials and reagents used include the whole blood genomics extraction kit (Tiangen Biochemical Technology Beijing Co., LTD), ABI 2720 Thermal Cycler (Applied Biosystems, Waltham, MA, USA), centrifuge model 581OR (Eppendorf (Hamburg, Germany)), XiangYi H1650-W (XiangYi, Hunan, China), the EP600 Gel electrophoresis meter (Shanghai Yubo Biotechnology Co., LTD.), the NanoDrop 2000 (NanoDrop Technologies, Wilmington, DE, USA), Invitrogen Qubit 3.0 Spectrophotometer (Invitrogen, Carlsbad, CA, USA), Illumina Hiseq/Nova seq (Illumina, CA, USA), the Agilent 2100 bioanalyzer (Agilent Technologies, USA), Herculase II Fusion DNA Polymerases (Agilent Technologies, CA, USA), TIANGEN Gel Extraction kit (TIANGEN, Beijing, China), 10X Reaction buffer and the Hot-start Taq polymerase (TaKaRa, Dalian, China).

2.4. Genotyping

The TM Multiple SNP Typing Kit (Shanghai Genesky Biotechnology) was used in this study for genotyping single nucleotide polymorphisms (SNPs). A ligase reaction with a high degree of specificity was utilized to identify the SNP allelic site. After that, the ligated products of different lengths were obtained by adding non-specific sequences of varying lengths at the end of the ligase probes, and a ligase addition reaction was performed. Following the amplification of the ligated products by PCR utilizing universal primers labeled with fluorescence, the products were separated by fluorescence capillary electrophoresis. Ultimately, the electrophoretic patterns were analyzed to determine the genotypes at each SNP locus.

2.5. Data analyses

The SPSS 26.0 software was utilized for analyses of statistical data. Measurement data were compared using the *t*-test and count data was analyzed using the chi-squared (χ^2) test. The Wilcoxon Rank-Sum test was conducted to examine the BMI. The Hardy-Weinberg equilibrium (HWE) was assessed using the chi-squared test or SHEsis program. The genotypic and allelic association with the disease was analyzed utilizing the PLINK program [27]. The Haploview v4.2 (Broad Institute, Cambridge, MA, United States) was utilized to produce a linkage disequilibrium (LD) plot [28]. PLINK was utilized to analyze haplotype associations. To derive the odds ratios (ORs) and the 95% confidence intervals (CIs), logistic regression was utilized, with the adjustment of covariates. In addition, the SNPs were examined employing three different logistic regression models: recessive, dominant, and additive. All tests were two-tailed, and the results were considered statistically significant at $P < 0.05$.

3. Results

3.1. Baseline characteristics

Table 1 illustrates the clinical features of the individuals who participated in this research. Among them, a comparison between gender, age, and smoking behavior showed statistical significance ($P < 0.05$). Hence, these factors were included in the subsequent logistic regression analysis as covariates. No statistical significance was found in the BMI, drinking, and special diet requirements between the LSCC patient group and the control group.

Table 1. Clinical characteristics of the collected LSCC population and controls

Characteristic	LSCC ($n = 60$)	Control ($n = 60$)	*P*
Gender (M/F)	56/4	30/30	< 0.001
Age, mean ± SD	62.85 ± 8.93	53.67 ± 14.71	< 0.001
BMI, mean ± SD	24.95 ± 3.57	25.88 ± 3.01	0.13
Drinking			
No	44	51	0.17
Yes	16	9	
Smoking			
No	20	45	< 0.001
Yes	40	15	
Special Diet Requirements			
No	49	56	0.09
Yes	11	4	

3.2. Hardy–Weinberg (HWE) analysis of the examined SNPs

The results of the HWE analysis indicated that neither the LSCC patients nor the controls had any deviations from HWE for the three markers, rs145135970, rs1799780, and rs25489.

3.3. Genotypic and allelic correlation with LSCC

In the LSCC population, the allelic frequencies and genotypic distribution of the 4 variants (rs145135970, rs1799780, rs25489, and rs72484243) exhibited considerable variation between the LSCC and control group ($P < 0.05$). However, only the allelic frequencies of GTGT at the rs72484243 locus demonstrated a significant difference in allelic distribution ($P = 0.02$, 95% CI = 1.09–4.16). Patients who had the GTGT genotype had a risk of developing LSCC that was 2.13 times higher than the controls. After controlling for the effects of sex, age, and smoking habits, additional logistic regressions were performed using the recessive, dominant, and additive models. A strong link between the rs72484243 locus and the risk of LSCC was discovered under the additive and dominant models. The GTGT allele was associated with a 2.74-fold higher risk of LSCC. These data are summarized in **Table 2** and **Table 3.**

The Manhanttan plot of the chi-squared allelic test is illustrated in **Figure 1**.

Table 2. Allelic association analysis between four SNPs and LSCC

SNP	Ref	Alt	Model	LSCC (11|10|00)	Control (11|10|00)	χ^2	OR (95%CI)	*P*
rs145135970	GTGTGTGT	-	Allele	5/115	13/103	4.15	0.34 (0.12–0.99)	0.04
rs1799780	G	A	Allele	5/115	15/101	5.84	0.29 (0.1–0.83)	0.02
rs25489	C	T	Allele	5/115	15/103	5.64	0.29 (0.1–0.85)	0.02
rs72484243	GTGT	-	Allele	31/89	16/98	5.07	2.13 (1.09–4.16)	0.02

Abbreviation: Reference allele, ref; altered allele, alt; number of homozygous mutations, heterozygous mutations, and homozygous normal in the sample, 11|10|00; the t-statistic of the coefficient, STAT.

Table 3. Logistic regression analysis of XRCC1 polymorphisms and risk of LSCC in our cohort

SNP	Allele	Model	OR (95%CI)	*P*
rs145135970	GTGTGT-	Additive model	0.31 (0.1–0.95)	0.04
		Dominant model	0.31 (0.1–0.95)	0.04
		Recessive model	NA	NA
rs1799780	G-A	Additive model	0.32 (0.11–0.91)	0.03
		Dominant model	0.31 (0.1–0.95)	0.04
		Recessive model	NA	NA
rs25489	C-T	Additive model	0.33 (0.12–0.92)	0.03
		Dominant model	0.32 (0.11–0.97)	0.04
		Recessive model	NA	NA
rs72484243	GTGT-	Additive model	2.74 (1.27–5.91)	0.01
		Dominant model	2.74 (1.27–5.91)	0.01
		Recessive model	NA	NA

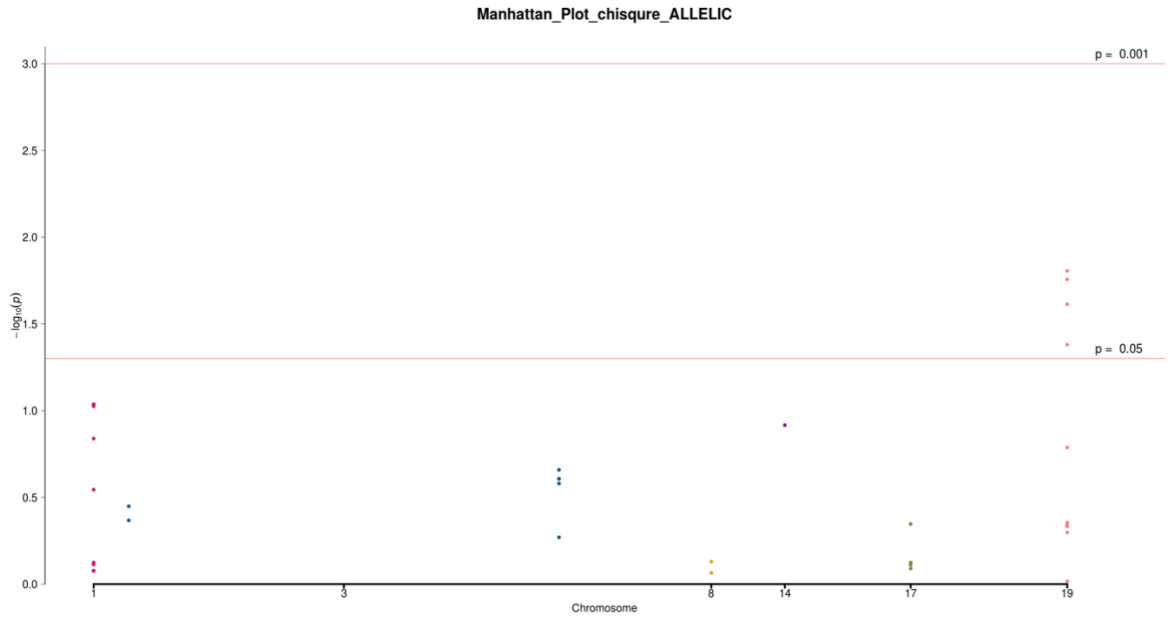

Figure 1. Manhattan plot of chi-squared allelic test

3.4 Haplotypes associated with LSCC

LD analysis indicated strong associations between rs25489 and rs1799780 with LSCC, where D' = 1, the logarithm of the odds (LOD) = 24.93, r^2 = 1, and Dist = 864 (**Table 4**). Three XRCC1 SNP loci were analyzed for haploid frequency, revealing four haplotypes at the three loci. However, the difference in the distribution of haplotypes GTGTGTGTGTGTGTCG and GTGTGTGTGTGTGTCA in the LSCC population was not statistically significant ($P > 0.05$). Conversely, the distribution of haplotypes-TA and GTGTGTGTGTGTGTTG were significantly different between both groups ($P < 0.05$). The risk of developing LSCC increased by 0.12 and 0.35 for the -TA and GTGTGTGTGTGTGTTG haplotype carriers respectively, as shown in **Table 5**.

The LD for the three SNPs that were studied in LSCC populations is depicted in **Figure B**.

Table 4. Association between SNPs with LSCC

SNPs	D' (95%CI)	LOD	r^2	Dist
rs145135970|rs25489	1 (0.87–1)	19.99	0.89	8918
rs145135970|rs1799780	1 (0.87–1)	19.92	0.89	9782
rs25489|rs1799780	1 (0.92–1)	24.93	1	864

Abbreviation: Linkage disequilibrium, LD; the value of D' (0~1) between the two loci, D', D'=D/Dmax; the log of the likelihood odds ratio, a measure of confidence in the value of D', LOD; the correlation coefficient between the two loci, r^2; the distance before the two SNPs, dist.

Table 5. Association of haplotypes with LSCC (logistic regression).

Haplotype	LSCC	Control	Estimate	SE	P-value	OR (95%CI)	SNPs
-TA	8 (6.67%)	19 (15.83%)	1.53	0.51	0.03	0.12 (0.01–1.07)	rs145135970|rs25489|rs1799780
GTGTCG	14 (11.67%)	18 (15.25%)	0.006	0.19	0.82	0.53 (0.37–1.62)	rs145135970|rs25489|rs1799780
GTGTTG	23 (19.17%)	11 (9.17%)	1.21	0.64	0.04	0.35 (0.01–1.21)	rs145135970|rs25489|rs1799780
GTGTCA	13 (10.83%)	17 (14.17%)	0.05	0.24	0.32	0.28 (0.01–0.6)	rs145135970|rs25489|rs1799780

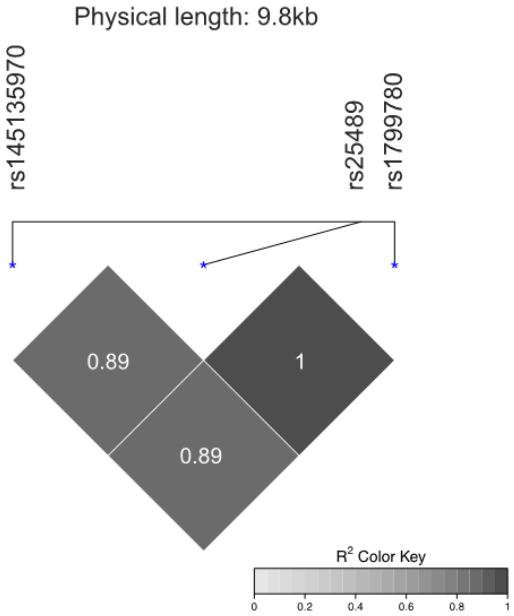

Figure 2. Depiction of LD for the three SNPs studied in LSCC populations

4. Discussion

This study demonstrated that the rs72484243 gene variants were linked to an increased LSCC risk in the population from northwest China. According to our knowledge, this is the first study that describes the link between the gene rs72484243 and the risk of LSCC.

As the most prevalent tumor of the upper respiratory tract, laryngeal cancer is a global health problem with a dismal prognosis and a high recurrence rate [29]. It is a set of head and neck cancers (HNC) that accounts for around 20% of all cancer cases. Unfortunately, laryngeal cancer is generally detected after it has already advanced to late stages [30]. Causes of laryngeal cancer primarily include smoking, alcohol consumption, HPV infection, and genetic predisposition [31–33]. In addition, having a family history of kidney and colorectal cancer was also associated with a greater risk of developing laryngeal cancer [34]. Numerous studies provided evidence that certain heritable factors have a role in the onset and progression of laryngeal cancer, including cyclin-dependent kinase, DNA repair gene, NER pathway gene, special AT-rich sequence-binding protein 1 and 2, B-cell translocation gene 1, matrix metalloproteinase 11, P14, epidermal growth factor-like domain 7 (Egfl7), and methylene tetrahydrofolate reductase [35–41].

There is a significant difference in LSCC survival rates based on factors like sex, age, stage of malignancy, and therapy measures [42–45]. The 5-year survival rate is > 90 % for patients who are in stages I or II, but is <60 % for patients who are in a locoregional advanced stage [46]. Researchers have discovered several genes involved in the DNA repair pathways for their potential involvement in the onset and progression of laryngeal cancer. Nevertheless, the findings were not conclusive. Therefore, patients with LSCC might benefit from the discovery of novel tumor biological markers that may aid in early diagnosis and therapy choices [47].

DNA repair is an essential mechanism in the protection of cells against carcinogenesis. Genomic instability may be triggered by environmental carcinogen-caused DNA damage. Therefore, alterations in DNA repair genes may affect an individual's susceptibility to cancer, as well as their therapeutic response and prognosis. The link between polymorphisms in the *XRCC1* gene Arg399Gln, *XRCC3* gene Thr241Met, and XPD was discovered through a meta-analysis. According to recent findings, DNA damage, which may be triggered by exposure to UV light, ionizing radiation, or environmental chemicals, is possibly the most critical factor that causes human malignancies [48]. The cell is stimulated to initiate the process of DNA repair when it experiences DNA damage. DNA repair systems are critical to maintaining genomic stability and are significantly involved in the prevention of mutations.

XRCC1 is a common DNA repair gene found on chromosome 19q13.2–13.3 that primarily functions in the process of DNA BER [49,50]. It is responsible for the formation of enzyme complexes that are optimized for the repair of single-strand breaks. In addition, it is also involved in other repair pathways by recruiting and organizing a vast number of enzymes in multi-step repair processes [51]. One of the XRCC1 polymorphisms, Arg399Gln (G to A; rs25487) on exon 10, has been linked to DNA repair impairment and high DNA adducts by altering XRCC1 protein functions [52]. The XRCC1 gene has also been linked to many different types of cancer, as well as diabetes and coronary artery disease [53–55]. Additionally, Arg399Gln XRCC1 is critical in the onset and progression of cervical cancer and endometriosis [50–56]. According to a previous study, SNPs in the coding region can affect DNA repair ability and are closely linked to the genetic susceptibility of many tumors, including HNC [57]. Amino acid substitution attributable to SNPs occurs most frequently at exonsArg194Trp, Arg280His, and Arg399Gln [58–60]. Protein-protein interactions involving XRCC1 and other BER proteins could be affected as a result of the amino acid alterations, which might alter DNA repair capabilities [58]. Previous studies have focused on the XRCC1 Arg399Gln SNP gene because of its association with an elevated risk of many malignancies, including HNC [61,62]. According to Wang *et al*., Arg399Gln variants of XRCC1 were linked

to a greater risk of HNSCC in Caucasians, as well as an enhanced risk of LSCC [60]. Conversely, Wu illustrated that polymorphism of XRCC1 Arg399Gln was not linked to an elevated risk of HNC [60]. XRCC-1 polymorphic hetero genotype (CT) and mutant genotype (TT) variants have been proven to be risk factors in loco-regionally progressed LSCC [63]. One meta-analysis that included 14586 participants showed that XRCC1 Arg399Gln variants (Arg/Gln and Arg/Arg+Arg/Gln) may increase the risk of HNC Caucasians [64].

We identified significant variations between LSCC and control groups in the genotypic and allelic frequencies of the rs72484243 locus. We discovered that the GTGT-genotype and the allele at the rs72484243 site of the XRCC1 gene were linked to the risk of LSCC in the population of Xinjiang China, which could be useful information for future clinical diagnosis and therapy. This study has some limitations. First, since only 60 people with LSCC in northwest China were included in this study, the findings may not be generalizable to the rest of the country and globally. Nevertheless, our findings provide a solid groundwork for future large-scale investigations. Secondly, this study only examined the polymorphism of the associated genes in LSCC patients, but not its role in the development of LSCC. Lastly, the candidate gene was selected based on the findings of relevant literature. Hence, validation is essential in future research.

5. Conclusion

Genetic polymorphisms of the XRCC1 gene at the rs72484243 site were associated with an elevated risk of LSCC among the Xinjiang population.

Funding

Natural Science Foundation of Xinjiang Uygur Autonomous Region (Grant Number: 2021D01C320).

Disclosure statement

The authors declare no conflict of interest.

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