RESEARCH ARTICLE

Genetic Association between the XPG Asp1104His Polymorphism and Head and Neck Cancer Susceptibility: Evidence Based on a Meta-Analysis

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Abstract

Background: Previous studies evaluating the association between the xeroderma pigmentosum group G (XPG) Asp1104His polymorphism and head and neck cancer susceptibility have proven controversial. This meta-analysis of the literature was performed to obtain a more precise estimation of the relationship. Materials and Methods: We systematically searched PubMed, Embase and Web of Science with a time limit of Dec 18, 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of any association. Results: We performed a meta-analysis of eight published case-control studies, including 3,621 cases and 5,475 controls. Overall, no significant association was found between the XPG Asp1104His polymorphism and head and neck cancer risk under all genetic models. In the subgroup analysis by ethnicity, the XPG Asp1104His polymorphism had statistically significant association with elevated head and neck cancer risk under CC vs GG (OR=1.24, 95% CI=1.00~1.54) and the recessive model (OR=1.22, 95% CI=1.01~1.46) in Asian populations. A similar result was found under CC vs GG (OR=1.22, 95% CI=1.01~1.47) in the population based subgroup by source of control. When performed by tumor site, the XPG Asp1104His polymorphism had statistically significant association with elevated laryngeal cancer under all genetic models (CC vs GG: OR=1.59, 95% CI=1.16~2.19; GC vs GG: OR=1.38, 95% CI=1.10~1.72; dominant model: OR=1.42, 95% CI=1.15~1.74; recessive model: OR=1.36, 95% CI=1.02~1.81). Conclusions: This meta-analysis suggested that the XPG Asp1104His polymorphism is a risk factor for head and neck cancer susceptibility, especially for laryngeal cancer and in Asian populations.

Keywords: XPG Asp1104His - polymorphism - head and neck cancer - meta-analysis

Asian Pac J Cancer Prev, 16 (9), 3645-3651

Introduction

Head and neck cancer (HNC), which includes cancers of the oral cavity, pharynx, hypopharynx, and larynx, is one of the most common cancers worldwide (Siegel et al., 2014). It accounts for nearly 3% of all incident malignancies in the United States with an estimated 52, 610 new cases and 11, 500 deaths from HNC in 2012 (Siegel et al., 2012). To date, there are ample evidences indicating that HNC is a complex multifactorial disorder involving genetic factors, lifestyle, tobacco smoke, alcohol consuming, and environmental factors (Shammaa et al., 2008; Liu et al., 2012; Mokhtari., 2012; Smith et al., 2012) and some low penetrant genes have been identified as potential HNC susceptibility genes (Hopkins et al., 2008; Arora et al., 2012).

Among them, an important one is the xeroderma pigmentosum group G (XPG) gene, also known as the excision repair cross complementing group 5 (ERCC5) gene, the XPG gene is located on chromosome 13q22-q33, encodes a 1186 amino-acid protein that functions as an endonuclease, cutting the DNA at the 3' terminus during the DNA repair process via the amino acids located in the N-terminus of the protein (Emmert et al., 2001; Clarkson, 2003). It is a member of the flap structure-specific endonuclease 1 (FEN1) family and encodes a protein of 1186 amino acids. The primary structure of human XPG protein harbors the N- and Inuclease domains that are highly conserved, which together form the nuclease core (Melis et al., 2013). Single nucleotide polymorphisms (SNPs) in XPG gene have been discovered in human populations, the Asp1104His polymorphism (rs17655 G>C) is common [minor allele frequency (MAF) >0.05] and regarded as a tagger, which was most frequently investigated for its association with cancer risk.

To date, molecular epidemiological studies have
investigated the relationship between the XPG Asp1104His polymorphism and predisposition to HNC. However, results of these studies are controversial; Therefore, we performed this meta-analysis in order to precisely assess the possible association of the XPG Asp1104His with the susceptibility to develop HNC.

Materials and Methods

Table 1. Characteristics of Case-Control Studies Included in the Meta-Analysis

| Study | Year | Country | Gene test | Source | Site | Case/Control | Case |
|-------|------|---------|-----------|--------|------|--------------|------|
| XPG His1104Asp | | | | | | |
| Lu B | 2014 | Asian | MassARRAY Analyzer | HB | Laryngeal | 176/176 | 53 | 69 | 54 |
| Li X | 2014 | Asian | Sequenom MassARRAY | HB | Laryngeal | 211/210 | 64 | 79 | 68 |
| Wyss AB | 2013 | Caucasian | Illumina GoldenGate assay | PB | head and neck | 915/1066 | 365 | 550 |
| Ma H | 2012 | Caucasian | ABI7900 sequence detection system | HB | head and neck | 1059/1056 | 359 | 52 |
| Yuan H | 2012 | Asian | ABI7900 sequence detection system | HB | head and neck | 394/884 | 108 | 191 | 95 |
| Abbasi R | 2009 | Caucasian | PCR-RFLP | PB | Laryngeal | 248/647 | 137 | 103 | 8 |
| Wen SX | 2006 | Asian | PCR-RFLP | HB | head and neck | 175/525 | 55 | 81 | 39 |
| Cui Y | 2006 | Caucasian | PCR-RFLP | PB | head and neck | 443/911 | 214 | 194 | 35 |

Search strategy
A systematic and electronic search of the PubMed, EMBASE and Web of Science was performed to identify studies using combinations of the following search terms: “head and neck cancer”, “oral cancer”, “oropharyngeal cancer”, “hypopharynx cancer”, “laryngeal cancer”, “pharyngeal cancer”, “cancer”, “tumor”, “carcinoma”, “nucleotide excision repair”, “XPG”, “ERCC5”, “polymorphism”, and “variation”. All of the studies were

*HB hospital based, PB population based; HWE: Hardy-Weinberg equilibrium; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism. NOS: Newcastle-Ottawa Scale

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DOI:http://dx.doi.org/10.7314/APJCP.2015.16.9.3645

Table 2. Main Results of Pooled Odds Ratios (OR) with Confidence Interval (CI) in the Meta-Analysis in Overall Population

| Polymorphism | Genetic model | Genetic type | Heterogeneity test | OR (95% CI) | P1 | Begg’s test | Egger’s test |
|--------------|---------------|--------------|--------------------|-------------|----|------------|-------------|
| XPG His1104Asp | Codominant model | CC vs GG | 15.2 | 60.50% | 0.02 | 1.11 (0.94–1.31) | 0.24 | 0.3 | 0.3 | 0.76 | 0.3 | 0.78 |
| | GC vs GG | 13.71 | 56.30% | 0.03 | 1.09 (0.98–1.21) | 0.12 | 0.9 | 0.37 | 0.46 | 0.67 |
| | Dominant model | CC+GC vs GG | 16.47 | 63.60% | 0.01 | 1.10 (0.99–1.22) | 0.07 | 0.9 | 0.37 | 0.91 | 0.41 |
| | Recessive model | CC vs GC+GG | 12.2 | 42.60% | 0.09 | 1.03 (0.92–1.16) | 0.57 | 1.11 | 0.27 | 0.59 | 0.58 |

*PH value for heterogeneity; Po value for OR; Pb value for Begg’s test; Pe value for Egger’s test; OR: Odds ratio; CI: Confidence interval.
Table 3. Main Results of Pooled Odds Ratios (OR) with Confidence Interval (CI) in the Meta-Analysis by Ethnicity, Source of Controls and Tumor Site

| Polymorphism | Subgroup (N) | Genetic type | Heterogeneity test | OR (95% CI) | P1 | Begg's test | Egger's test |
|--------------|-------------|--------------|-------------------|-------------|----|-------------|--------------|
|              |             |              | Q                 | F (%)       | PH | Z            | P2           | t            | P3          |
| Asp148Glu    | Asian (4)   | CC vs GG     | 11.27             | 73.40%      | 0.01| 1.24 (1.00–1.54) | 0.05| 1.7 | 0.09 | 6.05 | 0.28 |
|              |             | GC vs GG     | 11.62             | 74.20%      | 0.01| 1.03 (0.85–1.24) | 0.77| 1.02 | 0.31 | 3.85 | 0.51 |
|              |             | CC+GC vs GG  | 15.65             | 80.80%      | 0   | 1.11 (0.93–1.32) | 0.24| 1.02 | 0.31 | 5.69 | 0.43 |
|              | Caucasian (4) | CC vs GG     | 5.67             | 47.10%      | 0.13| 1.22 (1.01–1.46) | 0.04| 1.7 | 0.09 | 5.03 | 0.05 |
|              |             | CC vs GC+GG  | 1.39             | 0.00%       | 0.5 | 0.93 (0.71–1.22) | 0.58| 1.04 | 0.3  | -2.62| 0    |
|              | HB (5)      | CC vs GG     | 12.05             | 66.80%      | 0.02| 1.19 (0.98–1.43) | 0.08| 1.71 | 0.09 | 6.25 | 0.16 |
|              |             | GC vs GG     | 11.63             | 65.60%      | 0.02| 1.03 (0.90–1.17) | 0.64| 0.73 | 0.46 | 0.96 | 0.7  |
|              |             | CC vs GC+GG  | 15.94             | 74.90%      | 0   | 1.07 (0.95–1.21) | 0.28| 0.73 | 0.46 | 2.04 | 0.5  |
|              | PB (3)      | CC vs GG     | 6.45             | 38.00%      | 0.17| 1.17 (0.99–1.39) | 0.07| 2.2 | 0.03 | 4.65 | 0.08 |
|              |             | GC vs GG     | 1.1              | 9.10%       | 0.29| 0.86 (0.59–1.25) | 0.43| 0   | 1    | -2.61| -    |
|              |             | CC vs GC+GG  | 0.03             | 0.00%       | 0.87| 1.22 (1.01–1.47) | 0.04| 0   | 1    | 0.94 | -    |
|              | Laryngeal (3) | CC vs GG     | 1.92             | 42.60%      | 0.09| 0.92 (0.79–1.09) | 0.33| 1.04 | 0.3  | -1.46| 0.25 |
|              |             | GC vs GG     | 7.78             | 74.30%      | 0.02| 1.59 (1.16–2.19) | 0   | 0   | 1    | -7.91| 0.25 |
|              |             | CC+GC vs GG  | 1.04             | 0.00%       | 0.6 | 1.38 (1.10–1.72) | 0.01| 1.04 | 0.3  | 2.71 | 0.09 |
|              | Mixed (5)   | CC vs GG     | 3.86             | 48.20%      | 0.15| 1.42 (1.15–1.74) | 0   | 1.04 | 0.3  | 6.52 | 0.02 |
|              |             | GC vs GG     | 6.51             | 69.30%      | 0.04| 1.36 (1.02–1.81) | 0.04| 0   | 1    | -6.12| 0.21 |
|              |             | CC vs GC+GG  | 0.1              | 0.00%       | 0.99| 0.96 (0.79–1.18) | 0.7 | 0.34 | 0.73 | -0.22| 0.81 |
|              |             | GC vs GG     | 7.23             | 58.50%      | 0.07| 1.02 (0.90–1.15) | 0.8 | 1.02 | 0.31 | -3.7  | 0.27 |
|              |             | CC+GC vs GG  | 5.03             | 40.40%      | 0.17| 1.01 (0.90–1.34) | 0.84| 1.02 | 0.31 | -3.22| 0.26 |
|              |             | CC vs GC+GG  | 1.3              | 0.00%       | 0.86| 0.98 (0.86–1.12) | 0.78| 0.73 | 0.46 | 0.57 | 0.52 |

*N: number of studies; PH: P value for heterogeneity; Po: P value for OR; Pb: P value for Begg’s test; Pe: P value for Egger’s test; OR: Odds ratio; CI: Confidence interval

(Cui et al., 2006; Abbasi et al., 2009; Ma et al., 2012; Wyss et al., 2013) were conducted in Caucasians. Five studies (Wen et al., 2006; Ma et al., 2012; Yuan et al., 2012; Li et al., 2014; Lu et al., 2014) were hospital-based, three studies (Cui et al., 2006; Abbasi et al., 2009; Wyss et al., 2013) were population-based. Three studies (Abbasi et al., 2009; Li et al., 2014; Lu et al., 2014) was performed on laryngeal cancer, five studies (Cui et al., 2006; Wen et al., 2006; Ma et al., 2012; Yuan et al., 2012; Wyss et al., 2013) on mixed cancers. Consequently, we performed subgroup analysis by stratification of ethnicity, source of controls and cancer type. Details of subjects in these studies were outlined in Table 1. Studies with control not in Hardy-Weinberg equilibrium (HWE) were also considered for meta-analysis, but they were excluded in the sensitivity analysis (Minelli et al., 2008).

Main meta-analysis results

The main results of our meta-analysis under four distinct genetic models were listed in Table 2 and Table 3. Overall, the XPG Asp1104His polymorphism had no association with increased HNC risk under all four genetic models (CC vs GG: OR=1.11, 95% CI=0.94–1.31, P=0.02, Figuer 2A; GC vs GG: OR=1.09, 95% CI=0.98–1.21, 3648 Asian Pacific Journal of Cancer Prevention, Vol 16, 2015
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Figure 1. Study Selection Process for the Meta-Analysis

Figure 2. Odds ratios (ORs) for associations between the XPG Asp1104His polymorphism and HNC susceptibility. (A) Study ID: (B) OR and 95% CI; (C) P-value; (D) Weight.

Figure 3. Publication Bias in Studies of the Relation between the XPG Asp1104His polymorphism and HNC Susceptibility Under the Dominant Model and the Recessive Model. A funnel plot with pseudo-95% confidence limits (dashed lines) was used.

P=0.03, Figure 2B; dominant model: OR=1.10, 95% CI=0.99~1.22; P=0.01, Figure 2C; recessive model: OR=1.03, 95% CI=0.92~1.16, P=0.09, Figure 2D).

In the subgroup analysis by ethnicity, the XPG Asp1104His polymorphism had statistically significant association with elevated HNC risk under CC vs GG (OR=1.24, 95% CI=1.00~1.54) and the recessive model (OR=1.22, 95% CI=1.01~1.46) in Asian population.

In the subgroup analysis by source of control, the XPG Asp1104His polymorphism had statistically significant association with elevated HNC risk under CC vs GG (OR=1.22, 95% CI=1.01~1.47) in the population based
In the subgroup analysis by cancer type, the XPG Asp1104His polymorphism had statistically significant association with elevated laryngeal cancer under all genetic models (CC vs GG: OR=1.59, 95% CI=1.16~1.92, Figuer 2A; GC vs GG: OR=1.38, 95% CI=1.10~1.72, Figuer 2B; dominant model: OR=1.42, 95% CI=1.15~1.74, Figuer 2C; recessive model: OR=1.36, 95% CI=1.02~1.81, Figuer 2D).

Heterogeneity and sensitivity analysis

As showed in Table2 and Table 3, there was statistically heterogeneity among these studies in overall comparisons (P<0.05), in the stratified analysis by ethnicity, source of control and tumor site, heterogeneity was also found in Asian, hospital based population and laryngeal cancer, but not found in some models in Caucasian, population based population.

Publication bias

Begg’s funnel plot and Egger’s test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel asymmetry under the dominant model (Figuer 3A) and the recessive model (Figuer 3B). Egger’s test also showed that there was no statistical significance for the evaluation of publication bias (CC vs GG: P=0.78, GC vs GG: P=0.67, dominant model: P=0.41, recessive model: P=0.58).

Discussion

DNA repair mechanisms play a critical role in the protection of cells from DNA damage and in the maintenance of genomic integrity. The nucleotide excision repair (NER) pathway is the primary mechanism for removal of bulky adducts from DNA, and thus is an important part of the cellular defense against a large variety of structural unrelated DNA lesions; The NER pathway includes several steps: The first step for NER pathway involves damage recognition by a complex of bound proteins, including XPC; The next step involves unwinding of the DNA by a complex including XPD and removal of the damaged single-stranded nucleotide fragment by molecules including XPG, ERCC1, and XPF (Tse et al., 2008; Machado et al., 2014; McCullough et al., 2014).

XPG is a NER pathway gene with an important role in the repair of DNA damage induced by exposure to environmental and biological mutagens or normal cellular metabolism. The XPG deficiency leads to DNA repair incapability, genomic instability, gene transcription. Abnormality, and facilitates cancer development (Cheng et al., 2002). Single nucleotide polymorphism (SNP) is the most common genetic variant in the genome; subtle functional alterations in SNPs may result in significant biological outcomes (Bernig and Chanock, 2006). Several genetic association studies have connected XPG Asp1104His polymorphism with HNC risk in the recent decade. However, the results contradict each other. To shed light on the association between the XPG Asp1104His polymorphism and HNC risk, we performed a meta-analysis involving eight case-control studies (9, 096 subjects). The summary OR of all case-control studies suggested no overall association for all genetic models adopted. Subgroup analyses were performed according to ethnicity and source of control, the results revealed the XPG Asp1104His polymorphism had statistically significant association with elevated HNC risk in Asian population and in the population based subgroup. The relationship between the XPG Asp1104His polymorphism and HNC susceptibility might be affected by the tumor sites. Accordingly, we also performed stratified analysis in the laryngeal cancer group, the result of this subgroup analysis showed a significant association between the XPG Asp1104His polymorphism and the risk of laryngeal cancer under all genetic models.

Although we have put considerable efforts and resources into testing possible association between the XPG Asp1104His polymorphism and HNC risk, there are still some limitations inherited from the published studies. First, a common limitation of meta-analysis was heterogeneity, heterogeneity was often caused by variation in the environmental and genetic background of study participants, which was unavoidable when combing many studies, and we found evidence of study heterogeneity in our study, presumably because of the ethnicity, source of control and tumor site. Second, the controls were not uniformly defined. Some studies used a healthy population as the reference group, whereas others selected hospital patients without organic breast cancer as the reference group. Therefore, non-differential misclassification bias is possible because these studies may have included the control groups who have different risks of developing breast cancer. Third, the overall outcomes were based on unadjusted estimates, while a more precise evaluation should be adjusted by other co-variants including tobacco use, alcohol consumption, viral infection, and environment factors if individual data were available.

In conclusion, our meta-analysis suggested that the XPG Asp1104His polymorphism was a risk factor for HNC susceptibility, especially in laryngeal cancer and in Asian population. However, further studies with large sample sizes are needed to investigate the association between the XPG Asp1104His polymorphisms and HNC susceptibility.

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