The Significance of Exo1 K589E Polymorphism on Cancer Susceptibility: Evidence Based on a Meta-Analysis

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Abstract

The exonuclease1 (Exo1) gene is a key component of mismatch repair (MMR) by resecting the damaged strand, which is the only exonuclease involved in the human MMR system. The gene product is a member of the RAD2 nuclease family and functions in DNA replication, repair and recombination. However, whether Exo1 is required to activate MMR-dependent DNA repair genes (DDR) remains unknown, the conclusions of the Exo1 polymorphisms on cancer susceptibility studies were not consistent. We carried out a meta-analysis of 7 case-control studies to clarify the association between the Exo1 K589E polymorphism and cancer risk. Overall, a significant association of the Exo1 K589E polymorphism with cancer risk in all genetic models (Lys vs Glu: OR = 1.51, 95% CI: 1.39–1.99, P < 0.01; Glu/Lys vs Glu/Glu: OR = 1.43, 95% CI: 1.28–1.60, P < 0.01; Lys/Lys vs Glu/Glu: OR = 2.45, 95% CI: 1.90–3.17, P < 0.01; Lys/Lys vs Glu/Lys vs Glu/Glu: OR = 2.27, 95% CI: 1.79–2.89, P < 0.01). In the stratified analysis by ethnicity, significantly increased risk was observed in Asian population (Lys vs Glu: OR = 1.53, 95% CI: 1.39–1.69, P < 0.01; Glu/Lys vs Glu/Glu: OR = 1.50, 95% CI: 1.34–1.69, P < 0.01; Lys/Lys vs Glu/Glu: OR = 1.48, 95% CI: 1.84–3.34, P < 0.01; Lys/Lys vs Glu/Lys vs Glu/Glu: OR = 1.58, 95% CI: 1.41–1.78, P < 0.01; Glu/Glu vs Glu/Lys vs Lys/Lys: OR = 2.18, 95% CI: 1.62–2.93, P < 0.01). Subgroup analysis based on smoking suggested Exo1 K589E polymorphism conferred significant risk among smokers (Lys/Lys vs Glu/Lys vs Glu/Glu: OR = 2.16, 95% CI: 1.77–2.63, P < 0.01), but not in non-smokers (Lys/Lys vs Glu/Lys vs Glu/Glu: OR = 0.89, 95% CI: 0.64–1.24, P = 0.50). In conclusion, Exo1 K589E Lys allele may be used as a novel biomarker for cancer susceptibility, particularly in smokers.

Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [1]. In the United States, one fourth deaths are due to cancer [2]. The burden of cancer is increasing in economically developing countries as a result of population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices including smoking. Primary prevention strategies aim to reduce incidence, the early detection as subclinical cancer cases are discovered, which increases the chance of a cure in early stage patients or prolongs their survival time. However, most cancers are difficult to detect at their early stage, new markers for identifying high-risk populations as well as novel strategies for early detection are urgently needed. Now, mechanism of carcinogenesis is poorly understood. It has been suggested that susceptibility genes combining with environmental factors may be important in the development of cancer [3,4].

Individual variation in genetic backgrounds can in turn result in different consequences following the environmental exposure and may ultimately determine cancer risk. DNA repair genes form a complex network that protect the genome’s integrity from endogenous and exogenous damage [5]. When DNA damage is not repaired and does not induce apoptotic elimination of the cell, DNA defects accumulate and are propagated through the cell progeny, and finally cancer may occur [6,7]. Individual variations in DNA repair capacity due to the presence of polymorphisms in DNA repair-related genes may account for some cancer susceptibility in the general population [8,9]. Genetic polymorphisms of DNA repair genes have been reported to determine susceptibility to several cancers [10–15].

The exonuclease1 (Exo1) gene, located at chromosome 1q42–43, contains one untranslated exon followed by 13 coding exons and encodes an 846 amino acid protein [16,17]. The gene product is a member of the RAD2 nuclease family and functions in DNA replication, repair and recombination [18]. Exo1 is a key component of mismatch repair (MMR) by resecting the damaged strand, however, whether Exo1 is required to MMR-dependent DNA damage response (DDR) remains unknown [19]. The conclusions of the Exo1 polymorphisms on cancer susceptibility studies remain inconsistent, which is partially attributed to the heterogeneity of the cancer subtype, small sample size, and ethnicity of the patients.

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A guanine (G)/adenine (A) common single nucleotide polymorphism (SNP) at first position of codon 589 in exon 13 of Exo1 (dbSNP ID: rs 1047840), resulting in the substitution of a glutamic acid (Glu, E) residue (GAG) by lysine (Lys, K) residue (AAG) (also designated Exo1 K589E) in the exonic splicing enhancer (ESE), has been suggested to influence the products of Exo1 mRNA. To further determine whether there is an association of the Exo1 K589E with the risk for developing cancer, a comprehensive review and analysis of published data from different studies is needed.

In the present study, we have extensively reviewed literature and performed a meta-analysis based on all eligible case-control published data to evaluate the association between Exo1 K589E polymorphisms and cancer susceptibility.

**Materials and Methods**

**Identification of eligible studies**

A comprehensive literature search was conducted using the PubMed, Springer, Elsevier, CNKI (Chinese), and Wanfang (Chinese) Digital Dissertations Databases for relevant articles published in English and Chinese up to December 2013 with key words ‘K589E/rs1047840’, ‘Exo1 polymorphism’, and ‘cancer’. The full text of the candidate articles were examined carefully to determine whether they accorded with the inclusion criteria for the meta-analysis. The inclusion criteria were as follows: 1) about the Exo1 K589E polymorphism and cancer risk, 2) from a case-control designed study, 3) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI), and 4) genotype frequencies available.

The studies, in which the genotype of controls for a certain polymorphism was not consistent with Hardy-Weinberg equilibrium (HWE) were excluded from the analysis of this polymorphism.

**Data extraction**

Data were extracted independently by two investigators. For conflicting evaluations, an agreement was reached following discussion. If they could not reach a consensus, the third investigator was consulted to resolve the dispute, and a final decision was made by vote.

The following variables were extracted from each study if available: first author's name, publication year, cancer type, country of origin, ethnicity, study design, genotype distributions, and HWE of controls, respectively. Different ethnicity descents were categorized as Asian or Caucasian. Study design was stratified into hospital-based study and population-based study. If original genotype frequency data were unavailable in relevant articles, a request for additional data was sent to the corresponding author.

**Statistical analysis**

The analyses were conducted in Review Manager 5.0. The risks (ORs) of cancer associated with Exo1 K589E polymorphism were calculated directly from the data given in the eligible studies. OR corresponding to 95%CI was used to assess the strength of association between Exo1 K589E polymorphism and cancer. The pooled ORs were performed for allelic comparison (Lys vs Glu), heterozygote comparison (Glu/Lys vs Glu/Glu) and homozygote comparison (Lys/Lys vs Glu/GLu), dominant model (Lys/Lys+ Glu/Lys vs Glu/Glu), recessive model (Glu/Glu vs Glu/Lys+ Lys/Lys), respectively. Furthermore, studies were stratified according to ethnicity (Asian, Caucasian) and smoking status.

We assessed the departure from the HWE for the control group in each study using Pearson’s goodness-of-fit χ² test with 1 degree of freedom.

Heterogeneity in meta-analysis refers to the variation in study outcomes between different studies. Between-study heterogeneity was evaluated with a χ² based Q-test among the studies [20]. Heterogeneity was considered significant when $P<0.05$. In case of
no significant heterogeneity, point estimates and 95% CI was estimated using the fixed effect model (Mantel-Haenszel), otherwise, random effects model (DerSimonian Laird) was employed [21,22]. The significance of overall odds ratio (OR) was determined by the Z-test. If there were significant heterogeneity among included studies, the sources of heterogeneity would be explored using meta regression in Stata version 12.0 (http://www.stata.com).

To assess the stability of the results, one-way sensitivity analyses were performed to assess the stability of the results, in which a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. The publication bias was diagnosed by using inverted funnel plots, Begg’s test and the Egger’s test by Stata 12.0.

Statistical tests performed in the present analysis were considered significant whenever the corresponding null-hypothesis probability was $P<0.05$.

**Results**

**Study characteristics**

A total of 8 publications met the inclusion criteria [23–30], as summarized in Table 1 (the study selection process was shown in Figure 1). In one article [24], genotype of controls for a certain polymorphism was not consistent with HWE, therefore, it was excluded from the analysis. Hence, a total of 7 studies including 2,951 cases and 3,101 controls were used in the meta-analysis. All studies were case-control studies, including 7 studies on 7 cancer types. There were 5 studies of Asian descendent and 2 of Caucasian descendent. A classic PCR-RFLP assay was used in 6 out of 7 studies. One study was randomly repeated a portion of samples as quality control while genotyping.

**Quantitative synthesis**

The main results of this meta-analysis and the heterogeneity test were shown in Table 2 (Figure 2). We firstly analyzed the association in the overall population. Then in order to obtain the exact consequence of the relationship between Exo1 K589E polymorphism and cancer susceptibility, stratified analyses by ethnicity and smoking status were performed. When the Q-test of heterogeneity was not significant, we conducted analyses using the fixed effect models. The random effect models were conducted when we detected significant between-study heterogeneity.

In the overall analysis, we found a significant association between Exo1 K589E polymorphism and cancer risk in all genetic models (Lys vs Glu: OR = 1.51, 95% CI: 1.39–1.99, $P<0.01$; Glu/Lys vs Glu/Glu: OR = 1.43, 95% CI: 1.28–1.60, $P<0.01$; Lys/Lys vs Glu/Glu: OR = 2.45, 95% CI: 1.90–3.17, $P<0.01$; Lys/Lys + Glu/Lys vs Glu/Glu: OR = 1.53, 95% CI: 1.38–1.71, $P<0.01$; Glu/Glu vs Glu/Lys + Lys/Lys: OR = 2.27, 95% CI: 1.79–2.89, $P<0.01$).

Further stratification analysis by ethnicity, the results showed that Exo1 K589E polymorphism was significantly linked to cancer risk (table 3, figure 3). Overall, individuals carrying Lys allele had a subtly increased cancer risk among Asian population (Lys vs Glu: OR = 1.53, 95% CI: 1.39–1.99, $P<0.01$; Glu/Lys vs Glu/Glu: OR = 1.43, 95% CI: 1.28–1.60, $P<0.01$; Lys/Lys vs Glu/Glu: OR = 2.45, 95% CI: 1.90–3.17, $P<0.01$; Lys/Lys + Glu/Lys vs Glu/Glu: OR = 1.53, 95% CI: 1.38–1.71, $P<0.01$; Glu/Glu vs Glu/Lys + Lys/Lys: OR = 2.27, 95% CI: 1.79–2.89, $P<0.01$).

In Caucasian population, Exo1 K589E polymorphism was significantly associated with an increased risk in the allelic contrast, homozygote comparison and recessive model (Lys vs Glu: OR = 1.43, 95% CI: 1.14–1.79, $P<0.01$; Lys/Lys vs Glu/Glu: OR = 2.18, 95% CI: 1.62–2.93, $P<0.01$).

**Table 1. Characteristics of studies included in the meta-analysis.**

| First author | Year | Ethnicity | Cancer type       | Source of control | Genotyping       | Matching criteria | Case/Control | Quality control | Genotype | HWE |
|--------------|------|-----------|-------------------|-------------------|------------------|-------------------|--------------|-----------------|-----------|-----|
| Chang [23]   | 2008 | Caucasian | Glioma            | Population        | Chip             | Age; gender; ethnicity | 112/110      | NA              | 0.419     | NA |
| Jin [24]     | 2008 | Asian     | Lung cancer       | Population        | Chip             | Age; gender        | 500/517      | Y               | 0.030     | W   |
| Wang [25]    | 2008 | Asian     | Breast cancer     | Population        | PCR-RFLP         | Age; gender        | 1272/1272    | NA              | 0.926     | NA |
| Thr [26]     | 2009 | Asian     | Oral cancer       | Population        | PCR-RFLP         | Age; gender        | 680/680      | NA              | 0.636     | NA |
| Hsu [27]     | 2009 | Asian     | Gastric Cancer    | Population        | PCR-RFLP         | Age; gender        | 179/179      | NA              | 0.940     | NA |
| Luo [29]     | 2012 | Asian     | Cervical Cancer   | Population        | PCR-RFLP         | Age; gender        | 627/627      | Y               | 0.411     | Y  |
| Bayram [30]  | 2012 | Caucasian | Hepatocellular carcinoma | Population | PCR-RFLP         | Age; gender; smoking; alcohol consumption | 224/224 | NA              | 0.089     | NA |

$^a$: Quality control: Quality control was conducted when sample of cases and controls was genotyped; NA: not available.

$^b$: HWE: Hardy-Weinberg equilibrium in control.

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OR = 2.37, 95% CI: 1.44–3.97, \( P = 0.01 \); Glu/Glu vs Glu/Lys + Lys/Lys: OR = 2.48, 95% CI: 1.64–3.75, \( P = 0.01 \).

Subgroup analysis was also stratified by smoking status. Exo1 K589E polymorphism was significantly associated with an increased cancer risk in smokers (Lys/Lys + Glu/Lys vs Glu/Glu: OR = 2.16, 95% CI: 1.77–2.63, \( P < 0.01 \)), but no association was observed in non-smokers (Lys/Lys vs Glu/Lys/Glu: OR = 0.89, 95% CI: 0.64–1.24, \( P = 0.50 \)).

Evaluation of publication bias

Begg’s funnel plot and Egger’s test were performed to assess the publication bias of the currently available literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models (Figure 4). Then, the Egger’s test was used to provide statistical evidence for funnel plot symmetry (Table 4).

Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not materially altered, indicating that our results were statistically robust (data not shown).

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Table 2. Main results of pooled ORs of the Exo1 K589E polymorphisms on cancer risk in the meta-analysis.

| Comparisons                  | Cases | Controls | Heterogeneity test | Summary OR (95% CI) | Hypothesis test | Studies |
|------------------------------|-------|----------|--------------------|---------------------|----------------|---------|
|                              | n/N   | n/N      | Q      | P          | I² (%) | Z       | \( P \) |
| Lys vs Glu                   | 1494/589 | 1142/6202 | 6.79  | 0.34      | 12   | 1.51(1.39,1.99) | 9.11    | <0.01  | 7      |
| Glu/Lys vs Glu/Glu           | 1038/2723 | 914/2987 | 7.98  | 0.24      | 25   | 1.43(1.28,1.60) | 6.28    | <0.01  | 7      |
| Lys/Lys vs Glu/Glu           | 228/1913 | 114/2187 | 3.27  | 0.77      | 0    | 2.45(1.90,3.17) | 6.85    | <0.01  | 7      |
| Glu/Lys+Lys/Lys vs Glu/Glu   | 1266/2951 | 1208/3101 | 6.49  | 0.37      | 8    | 1.53(1.38,1.71) | 7.81    | <0.01  | 7      |
| Lys/Lys vs Glu/Lys+Glu/Lys   | 228/2951 | 114/3101 | 2.98  | 0.81      | 0    | 2.27(1.79,2.89) | 6.67    | <0.01  | 7      |

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Figure 2. Forest plot of cancer risk associated with Exo1 K589E for the homozygote comparison (Lys/Lys vs Glu/Glu). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study specific weight. The diamond represents the pooled OR and 95% CI.

Figure 3. Forest plot of cancer risk associated with Exo1 K589E for the dominant model (Lys/Lys + Glu/Lys vs Glu/Glu) in smokers. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study specific weight. The diamond represents the pooled OR and 95% CI.
Discussion

Exo1 is a member of the RAD2 family of nucleases and possesses 5’ to 3’ double-stranded DNA (dsDNA) exonuclease and 5’-flap endonuclease activities and functions in a number of important cellular pathways including DNA repair, replication, recombination, and telomere integrity [31]. Among the DNA repair system, Exo1 is the only exonuclease involved in the human MMR system, one of the major roles is the MMR system which is responsible for correcting mismatches between bases and small insertion or deletion loops [32,33]. Although many SNPs in NQO1, CYP1A1, ERCC4, EXO1, MSH2, XRCC1 and hOGG1 have been identified, only some of them have been extensively investigated in epidemiological studies [34], SNPs for which potential functional evidence in the development, progression and metastasis of cancer remains unknown, especially for Exo1 gene.

In the present study, we were first analyzed the association of Exo1 K589E of cancer from 7 studies. The pooled results revealed
that Exo1 K589E Lys allele was associated with an increased risk for developing cancer. Among Asian population, Exo1 K589E polymorphism was significantly associated with an increased cancer risk in all genetic models but not in the Caucasian population, this suggested that a possible ethnic difference in the genetic background. Subgroup analysis was stratified by smoking status, Exo1 K589E polymorphism was significantly associated with an increased cancer risk in smokers, but no significant association was observed in non-smokers. The reasonable explanation is cigarette smoking, a well-known origin of DNA damage, releases many DNA damage inducers to respiratory system and causes DNA damages to the cells. Therefore, people who have high-risk genetic variant, such as the Lys allele of K589E, and also smoking habits, the combined effect of genetic and environmental factors would synergistically increase their cancer susceptibilities.

Although meta-analysis is robust, our study still has some limitations. Firstly, lacking sufficient eligible studies limited our further stratified analysis on types of cancer. Secondly, for each selected case-control study, our results were based on unadjusted individual data were available. Thirdly, lack of the original data of selected case-control study, our results were based on unadjusted further stratified analysis on types of cancer. Secondly, for each genetic background. Subgroup analysis was stratified by smoking status, Exo1 K589E polymorphism was significantly associated with increased risk of cancer, especially in smokers. However, further well-designed studies in large cohort of different ethnic origins and cancer types are needed before the application of Exo1 K589E polymorphism as cancer biomarker in clinical settings and early cancer detection.

Supporting Information

Checklist S1 PRISMA Checklist. (DOC)

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Author Contributions

Conceived and designed the experiments: FJD CHS XZ. Performed the experiments: FJD XZ. Analyzed the data: FJD CHS. Contributed reagents/materials/analysis tools: CHS LPD XQZ. Wrote the paper: FJD SLC. Copied the manuscript: LPD SLC.

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Table 4. Publication bias of Exo1 K589E for Egger’s test.

| Comparisons | t     | p     | 95% CI     |
|-------------|-------|-------|------------|
| Lys vs Glu  | -0.82 | 0.451 | -3.906–2.020 |
| Glu/Lys vs Glu/Glu | -0.24 | 0.823 | -3.145–2.617 |
| Lys/Lys vs Glu/Glu | -0.94 | 0.390 | -3.137–1.457 |
| Glu/Lys=Lys/Lys vs Glu/Glu | -0.60 | 0.574 | -2.907–1.804 |
| Lys/Lys vs Glu/Glu/Glu/Lys | -0.12 | 0.906 | -2.796–2.538 |

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