XPC exon15 Lys939Gln variant increase susceptibility to prostate adenocarcinoma
Evidence based on 4306 patients and 4779 controls

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Abstract
Background: Previous studies have investigated the correlation between xeroderma pigmentosum complementation group C (XPC) variants and prostate adenocarcinoma (PA) risk. Nevertheless, research findings remain inconclusive.

Methods: We conducted a pooled analysis to obtain a more accurate estimation of the relationship on XPC exon15 Lys939Gln polymorphism with susceptibility to PA. Moreover, in silico tools were employed to investigate the effect of XPC expression on PA patients’ survival time.

Results: A total of 4306 patients and 4779 control subjects were assessed. The overall results indicated that XPC Lys939Gln variant was associated with PA risk (recessive genetic model: odds ratio = 1.15, 95% confidence interval = 1.02–1.30, P = .044, P = .021, F = 45.2), especially in Asian descendants. Population-based studies revealed similar results (odds ratio = 1.15, 95% confidence interval = 1.01–1.32, P = .040, F = 39.0). In silico tools showed that XPC expression in Caucasian patients was lower than in the normal group. No positive association was observed in African patients. PA subjects with high XPC expression had a longer overall survival time than low expression group.

Conclusion: Our findings indicated that XPC Lys939Gln variant might contribute to increased PA susceptibility, especially for Asian patients.

Abbreviations: HB = hospital based, HWE = Hardy–Weinberg equilibrium of controls, NA = not available, PA = prostate adenocarcinoma, PB = population based, XPC = xeroderma pigmentosum complementation group C, ZFYVE20 = Rabenosyn-5.

Keywords: analysis, prostate adenocarcinoma, variant, xeroderma pigmentosum complementation group C

1. Introduction
Prostate adenocarcinoma (PA) remains the most common malignancies among male worldwide. Previous studies showed that PA was the third and second major cause of male mortality in Europe and America.[12] National Cancer Institute estimated that approximately 164,690 new PA cases was diagnosed in 2018, with more than 3 million men suffering from this disease in the United States (https://seer.cancer.gov/csr/1975_2015). Although there are epidemiologic differences between the PA incidence and mortality rates in Western and Asian countries, the incidence rate of this cancer type in Asia has increased tremendously in recent years.[3,4] Until now, the detailed mechanisms and exact etiology of PA remains unclear.[5] In addition, the prevention and treatment for PA is still complicated depending on the stage of disease and the choice of single patient.[6] Therefore, it is urgent to update the molecular mechanism of PA pathogenesis and explore new targeted therapies.

It has been shown that genetic factors could play pivotal roles in the development of PA. For instance, a decline in DNA repair was reported as a key factor in the progression of PA.[7] Nucleotide excision repair (NER), the major defense mechanism of antimutagenic exposure, is known as the main DNA repair pathway in human.[8] Xeroderma pigmentosum complementation group C (XPC), an integral part of the NER pathway, can mediate the elimination of DNA damage and result in human carcinogenesis. One of the most extensively studied polymorphism of XPC is an A to C substitution at position 939, resulting in the replacement of lysine to glutamine (Lys939Gln, rs2228001).[12] Previous studies have shown that XPC Lys939Gln variant is a risk factor for bladder cancer,[13] colorectal cancer,[14] and lung...
cancer.\textsuperscript{15} Association between this polymorphism and PA risk has also been previously studied.\textsuperscript{16–20} However, the relationship between XPC Lys939Gln polymorphism and PA susceptibility in different case–control studies is not clear. Therefore, a comprehensive analysis based on all eligible data according to the inclusion criteria was performed to further explore the correlation between XPC Lys939Gln variant and PA risk.\textsuperscript{16–26}

2. Methods

2.1. Search strategy

A comprehensive literature search was conducted on electronic databases, such as Web of Science, Google Scholar, PubMed, and China Wanfang Databases to retrieve all publications on XPC exon15 Lys939Gln polymorphism and PA susceptibility. The following terms were employed: “XPC OR xeroderma pigmentosum complementation group C,” “polymorphism OR mutation OR variant,” and “carcinoma OR adenocarcinoma OR cancer.” Last search was performed on November 28, 2019. Furthermore, references of eligible publications were also screened to maximize the coverage of searches. If there were overlapping data based on the same population, we only selected the latest or the largest study.

2.2. Study selection and inclusion criteria

Two investigators independently screened the articles for compliance with inclusion criteria. Eligible studies in the current analysis should meet all the following criteria: investigated the relationship between XPC exon15 Lys939Gln polymorphism and PA risk; contained available genotype frequency for calculating odds ratio; and utilized a case–control design.

2.3. Exclusion criteria

The exclusion criteria were: studies without control data; articles did not contain available genotype frequency for pooled analysis; conference papers or reviews; and overlapping data from the same laboratories or authors.

2.4. Data extraction

All relevant data were independently assessed by two of the authors. The following information was extracted from each study: first authors’ name, publication year, ethnicity of participants, source of control, sample size of case and control group, genotyping data of XPC exon15 Lys939Gln polymorphism in cases and controls, age range, P value of Hardy–Weinberg equilibrium (HWE) in control, genotyping method. If the disagreement existed, it should be resolved by discussion with a 3rd investigator.

2.5. Methods for quantitative synthesis

The overall association between XPC exon15 Lys939Gln polymorphism and PA risk was calculated through odds ratio and 95% confidence interval (CI). Four genetic models were applied in the present analysis: allelic comparison (Gln-allele vs Lys-allele, or C-allele vs A-allele), homozygote contrast (Gln/Gln vs Lys/Lys), dominant genetic model (Gln/Gln + Gln/Lys vs Lys/Lys), and recessive model (Gln/Gln vs Gln/Lys + Lys/Lys). \(I^2\) test and \(Q\) test was adopted to assess \(P\) value of heterogeneity. If \(I^2 < 50\%\) or \(P\) value of \(Q\) test more than .005, the fixed-effects model (Mantel–Haenszel method) is employed. Otherwise, the random-effects model (DerSimonian–Laird method) would be conducted.\textsuperscript{27,28} The qualitative funnel plot was performed to investigate publication bias by measuring standard error of log (odds ratio [OR]) for single research plotted against its OR. HWE was measured by chi-square test. \(P\) value > .05 indicated an HWE balance. Stratified analysis contained types of ethnicity and source of control. The present analyses were carried out using STATA software v11.0 (Stata Corporation, Lakeway, TX).

2.6. Expression of XPC utilizing in silico analysis

We employed the online gene expression database to further evaluate the expression of XPC in PA tissues as well as the paracancerous tissues (http://gemini.cancer-pku.cn/).\textsuperscript{29} A total of 549 participants were included in this database for investigating the XPC expression in prostate tissues. The Cancer Genome Atlas (TCGA) samples were also applied to demonstrate the effect of high and low expression of XPC on PA risk and overall survival (OS) probability (http://genomics.jefferson.edu/proggene/intro.php). Furthermore, we adopt the online database (http://gepia.cancer-pku.cn/index.html) to explore the gene–gene correlation regarding XPC.

3. Results

3.1. Studies characteristics

As shown in Table 1, a total of 11 publications describing 12 case–control studies on XPC exon15 Lys939Gln polymorphism were eventually retrieved in the current analysis. The study conducted by Yang et al.\textsuperscript{30} contained overlapping data compared to that by Zhang et al.\textsuperscript{12,23} Therefore, we only choose the latest study by Zhang et al. A totally of 4306 PA patients and 4779 control subjects were enrolled in the current analysis. Moreover, we investigated minor allele frequencies of XPC Lys939Gln (rs2228001A/C) polymorphism reported in the main worldwide populations: in Africans, 0.249; Europeans, 0.405; Americans, 0.280; East Asians, 0.333; South Asians, 0.320; and Global, 0.315 (Fig. 1). In subgroup analysis by race, a total of 7 studies were based on Asian populations, 2 studies focused on Caucasian populations, and the rest focused on Arabians. In stratified analysis by source of control, there were 6 hospital-based studies and the rest 6 studies were performed utilizing population-based controls. Polymerase chain reaction-restriction fragment length polymorphism method was applied in 7 of the studies. The PRISMA checklist and flowchart have been uploaded in the supplementary material, http://links.lww.com/MD/E536, http://links.lww.com/MD/E537.

3.2. Quantitative synthesis

When all of the studies pooled together (Table 2), we observed a positive correlation between the XPC Lys939Gln variant and PA susceptibility in the recessive genetic model (OR = 1.15, 95% CI = 1.02–1.30, \(P_{\text{heterogeneity}} = .044, P = .021, I^2 = 45.2\%\)). In stratified analysis by ethnicity, a considerably increased risk was also observed in Asians (OR = 1.21, 95% CI = 1.01–1.43, \(P_{\text{heterogeneity}} = .008, P = .034, I^2 = 65.2\%\), Fig. 2). However, we found no obvious association between this polymorphism and PA risk in Caucasians (allele contrast: OR = 1.02, 95% CI = 0.93–1.11, \(P_{\text{heterogeneity}} = .617, P = .721, I^2 = 0\%\); Gln/Gln vs Lys/Lys: OR = 1.05, 95% CI = 0.87–1.28, \(P_{\text{heterogeneity}} = .658, P = .584\),
Table 1

| First author | Year | Origin | Ethnicity | Source | Case Control | HWE | Age range |
|--------------|------|--------|-----------|--------|--------------|-----|-----------|
| Hirata       | 2007 | Japan  | Asian     | HB     | 165 165      | 77 77 | 23 70 72 | 0.372 68±5.0 | 67±15 |
| Agalliu      | 2010 | USA    | Caucasians| PB    | 1577 1591 | 99 99 | 1 1 | 0.99 99.9 |
| Mandal       | 2012 | India  | Asian     | PB     | 192 224     | 71 93 16 | 94 114 | 0.570 62.6±8.9 | 59.1±10.4 |
| Mittal       | 2012 | India  | Asian     | PB     | 195 250     | 73 94 19 | 104 127 | 0.727 55±6.4 | 47±9.3 |
| Liu          | 2012 | China  | Asian     | HB     | 202 221     | 81 86 19 | 100 102 | 0.426 70.7±8.4 | 70.4±10.0 |
| Sorour       | 2013 | Egypt  | Arabian   | HB     | 50 50       | 9 16 5 | 27 18 | 0.263 68±8.7 | NA |
| Mandal       | 2013 | India  | Asian     | PB     | 192 224     | 71 93 16 | 94 114 | 0.570 62.6±8.9 | 59.1±10.4 |
| Zhang        | 2014 | China  | Asian     | HB     | 229 236     | 33 38 15 | 108 177 | <0.001 66.7±6.2 | 67.3±7.5 |
| Kahnamoee    | 2016 | Iran   | Asian     | HB     | 153 205     | 47 59 47 | 62 88 55 | 0.044 62.7±6.2 | 69.2 |
| Wang         | 2017 | China  | Asian     | HB     | 1004 1055   | 131 459 | 125 406 | 435 0.379 | NA |

I² = 0; dominant genetic model: OR = 1.00, 95% CI = 0.87–1.14, \( P_{\text{heterogeneity}} = 0.604 \), \( P = 0.953 \), \( I^2 = 0 \); Gln/Gln vs Gln/Lys + Lys/Lys: OR = 1.07, 95% CI = 0.90–1.27, \( P_{\text{heterogeneity}} = 0.783 \), \( P = 0.450 \), \( I^2 = 0 \). Additionally, no positive relationship was identified in African descendants (Gln-allele vs Lys-allele: OR = 0.97, 95% CI = 0.75–1.24, \( P_{\text{heterogeneity}} = 0.709 \), \( P = 0.785 \), \( I^2 = 0 \); Gln/Gln vs Lys/Lys: OR = 1.13, 95% CI = 0.64–2.00, \( P_{\text{heterogeneity}} = 0.560 \), \( P = 0.679 \), \( I^2 = 0 \); dominant model: OR = 0.82, 95% CI = 0.58–1.18, \( P_{\text{heterogeneity}} = 0.918 \), \( P = 0.287 \), \( I^2 = 0 \); recessive model: OR = 1.32, 95% CI = 0.77–2.25, \( P_{\text{heterogeneity}} = 0.422 \), \( P = 0.306 \), \( I^2 = 0 \). Furthermore, in subgroup analysis by source of control, a notable association of this XPC polymorphism was found in population based studies (Gln/Gln vs Gln/Lys + Lys/Lys: OR = 1.15, 95% CI = 1.01–1.32, \( P_{\text{heterogeneity}} = 0.146 \), \( P = 0.040 \), \( I^2 = 39.0 \), Fig. 3). No significant correlation was demonstrated in studies using hospital based controls (Gln-allele vs Lys-allele: OR = 1.03, 95% CI = 0.90–1.18, \( P_{\text{heterogeneity}} = 0.305 \), \( P = 0.660 \), \( I^2 = 16.8 \); Gln/Gln vs Lys/Lys: OR = 1.09, 95% CI = 0.83–1.42, \( P_{\text{heterogeneity}} = 0.602 \), \( P = 0.542 \), \( I^2 = 52.4 \); dominant model: OR = 0.98, 95% CI = 0.82–1.18, \( P_{\text{heterogeneity}} = 0.740 \), \( P = 0.858 \), \( I^2 = 0 \); recessive model: OR = 1.14, 95% CI = 0.89–1.46, \( P_{\text{heterogeneity}} = 0.037 \), \( P = 0.289 \), \( I^2 = 57.9 \).

3.3. Expression of XPC utilizing in silico analysis

In silico tool evaluated expression of XPC in 497 primary tumor and 52 normal tissues. The XPC expression was lower in PA tissues than in control group (\( P < 0.05 \), Fig. 5A). Similar results were observed in Caucasian individuals (\( P < 0.05 \), Transcript per million, TPM: Caucasians vs control = 25.082 vs 29.439), but not in Africans (\( P > 0.5 \), TPM: Africans vs control = 26.424 vs 29.439, Fig. 4). Furthermore, we investigated whether XPC expression influenced the OS rate in PA cases. As described in

Figure 1. Minor allele and major allele frequency of xeroderma pigmentosum complementation group C exon15 Lys939Gln in controls stratified by race. Vertical line = allele frequency, horizontal line = allele type.
Fig. 5B, PA subjects with high XPC expression had a longer OS time than low expression group \((P < .05)\). Moreover, online database was also employed to explore the gene–gene correlation of XPC. As shown in Fig. 6A, at least 24 genes participated in the crosstalk with XPC. The ZFYVE20 gene was predicted to be the most related gene (Fig. 6B). Nevertheless, there are few studies on their connection in PA, which are required to be demonstrated in the future studies.

3.4. Publication bias

We employed Begg funnel plot to investigate publication bias in the enrolled studies. No publication bias for the XPC Lys939Gln variant was identified among all the models. For Gln-allele vs Lys-allele: \( t = 0.57, P = .579 \); Gln/Gln vs Lys/Lys: \( t = 0.62, P = .548 \); dominant genetic model: \( t = 0.47, P = .646 \); recessive genetic model: \( t = 0.70, P = .498 \). The symmetry of funnel plot also demonstrated no evidence of publication bias in the current analysis (Fig. 7).

4. Discussion

The pathogenesis of PA remains complex. Previous studies have shown that genetic variants of DNA repair genes, including XPC could downregulate the DNA repair capacity.\(^{[12,31]}\) Decreased DNA repair capacity causes genetic instability and could contribute to PA susceptibility.\(^{[32,33]}\) Up to now, various case–control studies were carried out to evaluate whether the XPC exon15 Lys939Gln polymorphism confer individual’s PA risk. Nevertheless, previous studies have shown controversial results.\(^{[16–22]}\) A previous study based on Japanese population suggested that XPC Lys939Gln variant might be a risk factor for PA susceptibility.\(^{[16]}\) However, another study indicated no significant difference in the XPC Lys939Gln genotypes of PA participants and control subjects in Egyptian populations.\(^{[23]}\) In 2013, He et al carried out a meta-analysis and demonstrated an elevated colorectal, lung, and bladder cancer susceptibility associated with this variant, especially in Asian population.\(^{[24]}\) Two years later, another study showed no statistical difference
Figure 3. Forest plot of MM vs MW + WW genetic model of xeroderma pigmentosum complementation group C exon15 Lys939Gln polymorphism in subgroup analyses by source of control. CI = confidence interval, OR = odds ratio.

Figure 4. Association of xeroderma pigmentosum complementation group C expression based on sample types (A) and the overall survival probability (B) among prostate adenocarcinoma participants.
between XPC Lys939Gln polymorphism and PA risk.\[35\] With the emergence of new case–control studies, the current study aimed to summarize all eligible data to achieve more accurate conclusions.

In this study, a total of 4306 cases and 4779 control subjects were investigated to determine the role of XPC Lys939Gln variant in PA susceptibility. We found a statistically increased risk of PA in the overall analysis (OR = 1.15, 95% CI = 1.02–1.30, \(P = .021\)). In subgroup analysis by ethnicity, we observed a significantly elevated risk in Asian populations (OR = 1.21, 95% CI = 1.01–1.43, \(P = .034\)). A similar positive finding was obtained in studies using population based controls (OR = 1.15, 95% CI = 1.01–1.32, \(P = .040\)), in line with the results reported by He et al.\[34\] Furthermore, in silico analysis evaluated the expression of XPC in Caucasian and African participants and showed evidence that XPC expression was downregulated in Caucasian PA tissues compared to control subjects. However, no statistical difference was identified in African descendants. Although large amounts of resources have been invested to determine the basis of genetic susceptibility to PA, the development of genomic biomarkers that can be used to predict PA susceptibility has only recently begun to gain traction. In this case, several studies using metabolomics and proteomics techniques were conducted to investigate potential biomarkers for PA.\[36–39\] We evaluated whether the XPC expression influenced the OS probability of PA cases, which show evidence that PA subjects with high XPC expression had a longer OS time than low expression group. It is possible that the prognosis of PA could be predicted by testing the expression of XPC in PA patients.

Meta-analysis is a type of retrospective study that can be influenced by methodologic deficiencies of the enrolled studies, and some limitations should be mentioned. First, the number of included studies in our study remains small, especially for subgroup analyses. Second, some covariates and risk factors including age, tumor grade, and smoking status should be assessed to obtain more accurate results. We tried to further
evaluate the correlation between XPC Lys939Gln polymorphism and these factors; nevertheless, lacking of original data in the enrolled publications might have influenced the ultimate assessment. Last but not least, other factors such as gene–gene and variant–variant interactions should be considered. Said et al reported that XPC Lys939Gln variant was not associated with PA risk; however, combined analysis of Lys939Gln and XPC-PAT polymorphism indicated that individuals carrying XPC (Lys/Gln + PAT D/D) genotypes were associated with PA susceptibility compared to controls. On the contrary, our analysis has also some advantages. First, all eligible studies based on inclusion criteria were selected to assess the relationship between XPC Lys939Gln polymorphism and PA susceptibility. Hence, statistical power of the present analysis was strengthened. Second, Begg funnel plot showed no evidence of publication bias, indicating that conclusions from the above analyses were solid and trustworthy.

5. Conclusions

The present study suggested that XPC Lys939Gln variant might contribute to increased PA susceptibility, especially for Asian descendants. Similar findings were also obtained in population-based studies. XPC might be related to the prognosis of PA. Future large scale and well-designed studies with different ethnic descendants are necessary to validate our findings.

Author contributions

FQ and LZ contributed to the study design, LFZ, SLG and LS extracted the data, KX and LS drafted the manuscript, LFZ and ZZ prepared figures and tables, ZZ, QXS and LJZ revised the manuscript. All authors approved the final manuscript.

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