A meta-analysis of XPD/ERCC2 Lys751Gln polymorphism and melanoma susceptibility

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Abstract: We performed a comprehensive meta-analysis to determine the association between XPD/ERCC2 Lys751Gln polymorphism and melanoma susceptibility. Based on comprehensive searches of the MEDLINE, EMBASE and ISI Web of knowledge, China National Knowledge Infrastructure (CNKI) and Wanfang Database, we identified eligible studies about the association between XPD/ERCC2 Lys751Gln polymorphism and melanoma risk. A total of 5,961 cases and 8,669 controls in studies were included in this meta-analysis. All studies were conducted in Caucasian populations. Allele model (Lys vs. Gln: P = 0.53; OR = 0.98, 95% CI = 0.91-1.05), and homozygous model (Lys/Lys vs. Gln/Gln: P = 0.32; OR = 0.93, 95% CI = 0.81 to 1.07) did not show increased risk of developing melanoma. Similarly, dominant model (Lys/ Lys+Lys/Gln vs. Gln/Gln: P = 0.18; OR = 0.93, 95% CI = 0.83 to 1.03) and recessive model (Lys/ Lys vs. Lys/Gln+Gln/Gln: P = 0.73; OR = 0.98, 95% CI = 0.88 to 1.09) failed to show increased risk of developing melanoma. Our pooled data suggest that there was no evidence for a major role of XPD/ERCC2 Lys751Gln polymorphism in the pathogenesis of melanoma among Caucasian populations.

Keywords: XPD, ERCC2, melanoma, meta-analysis

Introduction

Melanoma is an aggressive neoplasm with increasing frequency in Caucasians [2]. It has been reported that melanoma incidence in Caucasians has increased 10-fold over past years [3]. A major environmental risk factor for melanoma is ultraviolet (UV) radiation as it causes severe DNA damage [4, 5]. Although UV causes severe DNA damage, only parts of populations develop the clinical disease. The nucleotide excision repair (NER) system is the major defense to ameliorate the effects of UV-light-induced DNA damage [6]. One important component of NER, xeroderma pigmentosum group D (XPD), is one of the seven XP genes (XPA-G) that operates in the four steps of NER: (i) lesion recognition, (ii) strand incision, (iii) damaged nucleotide displacement and (iv) gap filling [7]. The excision repair cross-complementing group 2 (ERCC2) gene (formerly named XPD) maps to chromosome 19q13.3 and codes for an 86.9 kDa protein with 761 amino acids [1]. XPD/ERCC2 Lys751Gln is an A to C mutation at the codon 751[lysine (Lys) to glycine (Gln)], resulting in a total change in the electronic configuration and functions of the protein [1]. Since DNA repair is central to maintaining genomic integrity, polymorphisms in the XPD/ERCC2 gene may contribute to variations in DNA repair capacity and may affect genetic susceptibility to cancer. It is of interest to evaluate whether the Lys751Gln polymorphism of the XPD/ERCC2 gene plays an essential role for melanoma risk. Although several previous studies have investigated the association between Lys751Gln polymorphism in XPD/ERCC2 gene and risk of melanoma, most of the study sizes were relatively small, and the results were not consistent [8-11]. The exact relationship between the XPD/ERCC2 Lys751Gln polymorphism and susceptibility to melanoma is not entirely established. Therefore, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the association between the XPD/ERCC2 Lys751Gln polymorphism and melanoma.
Methods

Publication search

The electronic databases MEDLINE, EMBASE and ISI Web of knowledge, China National Knowledge Infrastructure (CNKI) and Wanfang Database were searched for studies to include in the present meta-analysis, using the terms: “XPD”, “ERCC2”, “genotype”, “melanoma”, “polymorphism”, “rs13181”, “A35931C”, “Lys751-Gln” and “mutation”. An upper date limit of January 30, 2015 was used, but no earlier date limit was applied. The search was conducted without any restrictions on language but focused on studies that had been conducted on human subjects. Only published studies with full text articles were included.

Inclusion and exclusion criteria

Included studies in this meta-analysis met the following criteria: (a) a human study on the association between XPD/ERCC2 Lys751Gln polymorphism and the risks of melanoma; (b) containing available genotype data in cases and controls for estimating an odds ratio (OR) and 95% confidence interval (CI); (c) genotype distributions of control population were consistent with Hardy-Weinberg equilibrium (HWE). The exclusion criteria were: (a) reviews, letters, editorial articles and case reports; (b) studies on the association between other gene polymorphisms and melanoma risks.

Data extraction

The following information was extracted from each study: first author, year of publication, ethnicity of study population, and the number of melanoma cases and controls for the Lys751Gln genotype. We did not define a minimum number of patients as a criterion for a study’s inclusion in our meta-analysis.

Statistical analysis

The association between XPD/ERCC2 Lys751-Gln polymorphism and melanoma risks was estimated by calculating pooled ORs and 95% CI in the allele model (Lys vs. Gln), homozygous model (Lys/Lys vs. Gln/Gln), dominant model (Lys/Lys+Lys/Gln vs. Gln/Gln), and recessive model (Lys/Lys vs. Lys/Gln+Gln/Gln). The effect of the association was indicated as an odds ratio (OR) with its corresponding 95% confidence interval (CI). Pooled OR was estimated using fixed and random effects models. Heterogeneity between studies was tested using the Q statistic. Heterogeneity was considered statistically significant if P<0.10. Heterogeneity was quantified using the $I^2$ metric, which was independent of the number of studies in the meta-analysis ($I^2<25\%$ no heterogeneity; $I^2 = 25-50\%$ moderate heterogeneity; and $I^2>50\%$ large or extreme heterogeneity). An estimate of potential publication bias was performed using the funnel plot. All calculations were performed using Review Manager 5.0 and STATA10.0 software.

Results

Study characteristics

A total of 51 studies were retrieved through database searching. After reading the titles.

### Table 1. Study characteristics

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Source of controls</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Genotype frequency of cases/controls</th>
<th>HWE</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cases/controls</td>
<td>Lys/Lys (A/A)</td>
<td>Lys/Gln (A/C)</td>
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<tr>
<td>Baccarelli</td>
<td>2004</td>
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<td>58/59</td>
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<tr>
<td>Debnik</td>
<td>2006</td>
<td>Population</td>
<td>Caucasian</td>
<td>426/421</td>
<td>146/161</td>
<td>207/196</td>
</tr>
<tr>
<td>Figl</td>
<td>2010</td>
<td>Population</td>
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<td>1186/1274</td>
<td>513/484</td>
<td>527/627</td>
</tr>
<tr>
<td>Han</td>
<td>2005</td>
<td>Population</td>
<td>Caucasian</td>
<td>203/844</td>
<td>81/295</td>
<td>99/415</td>
</tr>
<tr>
<td>Ibarrola-Villava</td>
<td>2011</td>
<td>Population</td>
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<td>240/157</td>
<td>281/186</td>
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<tr>
<td>Kertat</td>
<td>2008</td>
<td>Population</td>
<td>Caucasian</td>
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<td>78/82</td>
<td>122/135</td>
</tr>
<tr>
<td>Li</td>
<td>2006</td>
<td>Population</td>
<td>Caucasian</td>
<td>602/603</td>
<td>219/255</td>
<td>297/270</td>
</tr>
<tr>
<td>Millikan</td>
<td>2005</td>
<td>Population</td>
<td>Caucasian</td>
<td>1212/2436</td>
<td>441/981</td>
<td>576/1128</td>
</tr>
<tr>
<td>Paszkowska-Szczur</td>
<td>2013</td>
<td>Population</td>
<td>Caucasian</td>
<td>689/1635</td>
<td>245/592</td>
<td>325/767</td>
</tr>
<tr>
<td>Povey</td>
<td>2007</td>
<td>Population</td>
<td>Caucasian</td>
<td>507/438</td>
<td>242/206</td>
<td>200/177</td>
</tr>
<tr>
<td>Winsey</td>
<td>2000</td>
<td>Population</td>
<td>Caucasian</td>
<td>125/211</td>
<td>47/72</td>
<td>54/107</td>
</tr>
</tbody>
</table>
XPD/ERCC2 and melanoma

and abstracts, 13 potential studies were identified for further investigation [8-20]. One study was excluded for no available genotype data [11]. One case-control study was excluded for being not consistent with HWE [12]. Finally, 11 studies were included for data extraction [8-10, 13-20]. The studies were published between 2000 and 2013 (Table 1). The 11 studies provided 5,961 cases and 8,669 controls for XPD/ERCC2 Lys751Gln polymorphism. All studies were conducted in Caucasian populations. For case groups, the frequency of Lys/Lys-homozygous individuals was 67.1%. However, 29.1% of Lys/Gln-heterozygous individuals and 3.8% of Gln/Gln-homozygous individuals displayed the Lys751Gln polymorphism. In control groups, the frequencies of Lys/Lys-homozygous individuals, Lys/Gln-heterozygous individuals, and Gln/Gln-homozygous individuals were 68.5%, 27.9%, and 3.6%, respectively. The Lys allelic frequencies in the case and control groups were 81.7% and 82.5%, respectively.

Meta-analysis results

A total of 5,961 cases and 8,669 controls in 11 studies were pooled together for evaluation of the overall association between XPD/ERCC2 Lys751Gln polymorphism and risk of melanoma, the pooled OR indicated non significance association between the XPD/ERCC2 Lys751Gln polymorphism and susceptibility to melanoma. Allele model (Lys vs. Gln: P = 0.53; OR = 0.98, 95% CI = 0.91-1.05, Figure 1A), and homozgyous model (Lys/ Lys vs. Gln/ Gln: P = 0.32; OR = 0.93, 95% CI = 0.81 to 1.07, Figure 1B) did not show increased risk of devel-

Figure 1. Odds ratio with its 95% confidence interval of the association between XPD/ERCC2 Lys751Gln polymorphism and susceptibility to melanoma. A. Allele model. B. Homozygous model. C. Dominant model. D. Recessive model.
oping melanoma. Similarly, dominant model (Lys/ Lys+Lys/Gln vs. Gln/Gln: \( P = 0.18; \) OR = 0.93, 95% CI = 0.83 to 1.03, Figure 1C) and recessive model (Lys/Lys vs. Lys/Gln+Gln/Gln: \( P = 0.73; \) OR = 0.98, 95% CI = 0.88 to 1.09, Figure 1D) failed to show increased risk of developing melanoma. Moderate heterogeneity \( (I^2 = 50\%, \ P = 0.03) \) was found.

**Publication bias**

Begg-Mazumdar test and the Egger test were performed to assess the publication bias in the literature. All of the studies investigating the 751Lys allele versus the Gln allele yielded a Begg’s test score of \( P = 0.323 \) and an Egger’s test score of \( P = 0.412 \). These results do not indicate a potential for publication bias.

**Discussion**

In the present meta-analysis, we summarized all of the available data on the association between XPD/ERCC2 Lys751Gln polymorphism and melanoma. Our results do not indicate evidence for an association between XPD/ERCC2 Lys751Gln polymorphism and the risk of pathogenesis in melanoma among Caucasians.

Melanoma incidence has continuously increased worldwide in association with some well-known risk factors such as UV exposure and mutations in the CDKN2A gene, besides the possible contribution of some environmental and genetic factors [12]. The majority of the studies of melanoma were carried out in Europe, North America and Australia, with mainly Caucasian populations in geographic regions where the UV index is lower due to high latitude, except in Australia. People are exposed throughout the year to high-intensity solar radiation and high UV indices, critical factors to the development of skin cancers, including melanoma [21].

Three previous meta-analyses have reported there is a significant association between XPD/ERCC2 Lys751Gln polymorphism and susceptibility to melanoma [22-24]. A major concern is that an electronic search revealed several studies that were not included yet fall within the search criteria described, leading to the different results from our research.

Some limitations of this meta-analysis should be addressed. First, our results are based on unadjusted estimates. We should conduct the analyses by adjusting for age, gender and nationality. Our unadjusted results calculated from the genotype data were different from Figl et al. publication [14]. Second, the heterogeneity among the trials could be another limitation of our meta-analysis, although we applied both a random-effects model and a fixed-effects model to combine the data. However, as the number of trials was limited, careful interpretation of the heterogeneity is necessary. Therefore, we must explicitly state that caution is highly advisable when interpreting our results.

In conclusion, our pooled data suggest that there was no evidence for a major role of XPD/ERCC2 Lys751Gln polymorphism in the pathogenesis of melanoma among Caucasian populations.

**Disclosure of conflict of interest**

None.

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