XPD Lys751Gln and Asp312Asn Polymorphisms and Susceptibility to Skin Cancer: A Meta-Analysis of 17 Case-control Studies

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Abstract

Background: Numerous studies have explored the influence of XPD Lys751Gln and/or Asp312Asn polymorphisms on skin cancer susceptibility. However, the results remain inconclusive. To derive a more precise estimation, we conducted a comprehensive search to identify all available published studies and performed a meta-analysis. Materials and Methods: Electronic literature searches of the PubMed, CBM and CNKI databases were performed up to March 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were applied to assess the strength of associations. Results: Seventeen case-control studies were included with a total sample size of 6,113 cases and 11,074 controls for the XPD Lys751Gln polymorphism, and 10 studies (3,840 cases and 7,637 controls) for the XPD Asp312Asn polymorphism were pooled for analysis. Overall, no significant associations were found between the XPD Lys751Gln polymorphism and skin cancer risk in any genetic model. On stratified analysis by tumor type, XPD Lys751Gln polymorphism was not associated with increased risk of non-melanoma skin cancer, but was significantly related with increased risk of cutaneous melanoma (Gln/Gln vs Lys/Lys: OR=1.15, 95% CI=1.02-1.29, \( p = 0.023 \); dominant model: OR=1.09, 95% CI=1.01-1.18, \( p = 0.036 \)). For the XPD Asp312Asn polymorphism, no significant association with skin cancer risk was observed in overall or subgroup analyses. Conclusions: The present meta-analysis suggests that the XPD Lys751Gln polymorphism may contribute to the risk of cutaneous melanoma from currently available evidence. Further investigations are needed to obtain more insight into possible roles of these two polymorphisms in skin carcinogenesis.

Keywords: XPD - Lys751Gln - Asp312Asn - polymorphisms - skin cancer - meta-analysis

Introduction

Skin cancer, one of the most common neoplasms, has been an important public health problem in most Caucasian populations with the increasing incidence during the last few years (Leiter and Garbe, 2008). Statistics show that more than two million cases of skin cancer are diagnosed in America every year (Siegel et al., 2012). According to histological types, skin cancer can be subdivided into cutaneous melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), respectively (Rubin et al., 2005; Thompson et al., 2005).

Skin cancer has a complex etiology and pathogenesis caused by the interaction of environmental and inherited factors (Ji et al., 2012). It is widely accepted that inappropriate exposure to ultraviolet radiation (UVR) which causes various kinds of DNA damage, is critical in the occurrence and development of skin cancer (Armstrong et al., 2001). In addition, extensive epidemiological evidence has revealed that the incidence of skin cancer is variable in noncancer subjects with different ethnic backgrounds, suggesting host genetic susceptibility plays an important role in skin cancer risk among different ethnicities (Capell et al., 2009; Lin et al., 2011).

Xeroderma pigmentosum group D (XPD), also named excision repair cross-complementing rodent repair deficiency Group 2 (ERCC2), is one of the most important DNA repair genes. It plays a vital role in nucleotide excision repair (NER) pathway, which removes bulky adducts, such as those caused by environmental agents, UVR induced DNA damage, crosslinks and oxidative damage (Sancar et al., 1993; Weeda et al., 1993). Several important single-nucleotide polymorphisms (SNPs) have been identified in the XPD locus. Among them, Lys751Gln and Asp312Asn polymorphisms were most extensively investigated. The XPD Lys751Gln polymorphism (rs13181) in codon 751 of exon 23, an A to C substitution, results in a Lys to Gln amino acid exchange (Shen et al., 1998; Pabalan et al., 2010). And Asp312Asn polymorphism (rs1799793), a G to A substitution in codon...
312 of exon 10, produces Asp to Asn amino acid exchange (Shen et al., 1998; Pabalan et al., 2010).

To date, plenty of studies have explored the associations of XPD Lys751Gln and/or Asp312Asn polymorphisms with skin cancer susceptibility. Nevertheless, findings on the direction of the associations remain equivocal. To derive a more precise estimation, we conducted a comprehensive search to identify all available published studies and performed this meta-analysis.

Materials and Methods

Identification and eligibility of studies

Eligible articles up to March 2014 were identified by searching the electronic literatures of PubMed, CBM (Chinese Biomedical) and CNKI (China National Knowledge Infrastructure) databases. The search terms were used as follows: “xeroderma pigmentosum group D”, “XPD”, “ERCC2”, “cutaneous melanoma”, “basal cell carcinoma”, “squamous cell carcinoma of skin” and combined phrases. There were not any restrictions on sample size, population, or language. All eligible studies were retrieved, and their bibliographies were checked as well for other relevant publications. Studies were required to comply with the following inclusion criteria: (1) case-control studies; (2) the studies should evaluate the association of XPD Lys751Gln and/or Asp312Asn polymorphisms with skin cancer; (3) sufficient information to calculate odds ratios (ORs) with 95% confidence intervals (CIs); (4) For multiple publications reporting on overlapping data, only the most recent, largest or complete study was selected; and (5) the distributions of genotypes among controls conformed to the Hardy-Weinberg equilibrium (HWE) (Salanti et al., 2005).

Data extraction

Data of eligible studies were carefully extracted by two independent authors (HZ and JB) according to pre-specified selection criteria. A consensus meeting was then held to resolve any discrepancies. The following information was collected: name of the first author, publication year, ethnicity, country, number of cases and controls, distributions of every genotype, tumor type and P value for Hardy-Weinberg equilibrium (HWE).

Statistical analysis

All statistical analyses were performed using Stata statistical software, version 12.0 (Stata Corp, College Station, TX, USA). The chi-square goodness of fit was used to test deviation from HWE, statistical significance was defined as p < 0.05.

The crude odds ratios (ORs), as well as their 95% confidence intervals (95% CIs) were calculated to assess the strength of associations between XPD Lys751Gln and/or Asp312Asn polymorphisms with skin cancer risk. The pooled ORs were performed with codominant model (Lys/Gln vs Lys/Lys and Asp/Asn vs Asp/Asp; Gln/Gln vs Lys/Lys and Asn/Asn vs Asp/Asp), dominant model (Lys/Gln + Gln/Gln vs Lys/Lys and Asp/Asn + Asn/Asn vs Asp/Asp) and recessive model (Gln/Gln vs Lys/Gln + Lys/Lys and Asn/Asn vs Asp/Asn + Asp/Asp), respectively.

Heterogeneity among the studies in terms of degree of association was assessed using χ² tests. The I² statistic was used to estimate the percentage of variation between the results that was caused by heterogeneity, rather than sampling error (p<0.10 or I² >50% was treated as significant heterogeneity). When heterogeneity was detected, the random-effects model (DerSimonian-Laird method) (DerSimonian et al., 1986) was used to calculate the pooled ORs; otherwise, the fixed-effects model (Mantel-Haenszel method) was selected (Mantel et al., 1959). To evaluate the tumor type-specific effects, subgroup analysis was performed by tumor type. Sensitivity analyses were performed to see whether any exclusion of the studies could affect the initial results.

Moreover, potential publication bias was observed and evaluated by visual inspection of the Beggs’s funnel plots. We also employed the Beggs’s adjusted correlation test (Begg et al., 1994) to evaluate the possible publication bias (p<0.05 was considered representative of statistically significant publication bias).

Results

Study selection and characteristics

Based on the search terms, 58 individual literatures were initially found in the selected databases. After screening the titles and abstracts, only 20 potentially eligible articles were identified for further detailed evaluation. After full-text assessment of these articles, we included a total of 15 articles (Dybdahl et al., 1999; Winsey et al., 2000; Vogel et al., 2001; Yin et al., 2003; Baccarelli et al., 2004; Lovatt et al., 2005; Fest et al., 2005; Han et al., 2005; Thirumaran et al., 2006; Li et al., 2006; Millikan et al., 2006; Debniak et al., 2006; Povey et al., 2007; Kertat et al., 2008; Paszkowska-Szczur et al., 2013) in this meta analysis, including 9 studies for cutaneous melanoma (Winsey et al., 2000; Baccarelli et al., 2004; Han et al., 2005; Li et al., 2006; Millikan et al., 2006; Debniak et al., 2006; Povey et al., 2007; Kertat et al., 2008; Paszkowska-Szczur et al., 2013), 7 studies for basal cell carcinoma (Dybdahl et al., 1999; Vogel et al., 2001; Yin et al., 2003; Lovatt et al., 2005; Fest et al., 2005; Han et al., 2005; Thirumaran et al., 2006) and 1 for squamous cell carcinoma (Han et al., 2005). All articles were written in English. A flow diagram of the search process was shown in Figure 1.

![Figure 1. Flow Diagram of the Study Selection Process](image-url)
Concerning XPD Lys751Gln polymorphisms, 17 studies of the included 15 articles were eligible with a total sample size of 6113 cases and 11074 controls. With respect to XPD Asp312Asn polymorphism, 10 studies were pooled for analysis (3840 cases and 7637 controls). The characteristics of included studies were presented in Table 1 and Table 2.

**Meta-analysis results**

For all included studies, the allelic distributions of Lys751Gln and Asp312Asn in the control group were consistent with HWE at the 0.05 level (Table 1-2), indicating that obvious effects of natural selection and migration on genetic equilibrium had been avoided.

The association between XPD Lys751Gln polymorphism and skin cancer was shown in Table 3. The heterogeneity for all studies was only significant in dominant model (I²=34.6, p=0.080), so the random-effects model was used. The fixed-effects model was performed in other genetic models. No association was observed between the polymorphism and skin cancer for overall population at all genetic contrasts (Lys/ Gln).

### Table 1. Characteristics of the Studies of XPD Lys751Gln Polymorphism and Susceptibility to Skin Cancer

| First author | Ethnicity | Country | Sample Size | Genotype Distributions | Tumor type | P_HWE |
|--------------|-----------|---------|-------------|------------------------|------------|-------|
|             |           |         |             | Case/Control           |            |       |
|             |           |         |             | Lys/Lys | Lys/ Gln | Gln/Gln | Lys/Lys | Lys/ Gln | Gln/Gln |
| Dybdahl (1999) | Caucasian | Denmark | 40/40 | 21/17 | 2/16 | 7 | BCC | 0.65 |
| Winsey (2000) | Caucasian | UK | 125/211 | 47/54 | 24/72 | 107/32 | melanoma | 0.75 |
| Vogel (2001) | Caucasian | Denmark | 71/117 | 24/35 | 12/44 | 61/12 | BCC | 0.39 |
| Yin (2003) | Caucasian | Denmark | 20/20 | 10/9 | 1/8 | 4 | BCC | 0.86 |
| Baccarelli (2004) | Italian | Italy | 176/177 | 58/94 | 24/59 | 85/33 | melanoma | 0.92 |
| Han (2005a) | Caucasian | USA | 203/844 | 81/99 | 23/295 | 415/134 | melanoma | 0.84 |
| Han (2005b) | Caucasian | USA | 286/844 | 98/141 | 47/295 | 415/134 | BCC | 0.84 |
| Han (2005c) | Caucasian | USA | 280/844 | 126/112 | 42/295 | 415/134 | SCC | 0.84 |
| Lovatt (2005) | Caucasian | UK | 509/379 | 217/216 | 74/149 | 177/53 | BCC | 0.99 |
| Festa (2005) | Caucasian | Sweden | 197/561 | 69/94 | 34/194 | 285/85 | BCC | 0.57 |
| Li (2006) | Caucasian | USA | 602/603 | 219/297 | 86/255 | 270/78 | melanoma | 0.89 |
| Millikan (2006) | Caucasian | USA | 1212/2436 | 441/576 | 195/981 | 1128/327 | melanoma | 0.99 |
| Debniak (2006) | Caucasian | Poland | 426/1141 | 146/207 | 73/432 | 547/162 | melanoma | 0.87 |
| Thirumaran (2006) | Caucasian | Hungary | 529/533 | 174/269 | 86/179 | 262/92 | BCC | 0.97 |
| Povey (2007) | Caucasian | UK | 507/438 | 242/200 | 65/206 | 177/55 | melanoma | 0.22 |
| Kertat (2008) | Caucasian | Sweden | 241/251 | 78/122 | 41/82 | 135/34 | melanoma | 0.18 |
| Paszkowska-Szczur (2013) | Caucasian | Poland | 689/1635 | 245/325 | 119/592 | 767/276 | melanoma | 0.59 |

**Table 2. Characteristics of the Studies of XPD Asp312Asn Polymorphism and Susceptibility to Skin Cancer**

| First author | Ethnicity | Country | Sample Size | Genotype Distributions | Tumor type | P_HWE |
|--------------|-----------|---------|-------------|------------------------|------------|-------|
|             |           |         |             | Case/Control           |            |       |
|             |           |         |             | Asp/Asp | Asp/Asn | Asn/Asn | Asp/Asp | Asp/Asn | Asn/Asn |
| Winsey (2000) | Caucasian | UK | 125/211 | 49/54 | 22/89 | 95/27 | melanoma | 0.98 |
| Vogel (2001) | Caucasian | Denmark | 68/105 | 29/25 | 14/46 | 39/20 | BCC | 0.1 |
| Baccarelli (2004) | Italian | Italy | 164/172 | 52/94 | 18/59 | 89/24 | melanoma | 0.58 |
| Han (2005a) | Caucasian | USA | 206/836 | 88/99 | 19/342 | 373/121 | melanoma | 0.5 |
| Han (2005b) | Caucasian | USA | 285/836 | 104/149 | 32/342 | 373/121 | BCC | 0.5 |
| Han (2005c) | Caucasian | USA | 280/836 | 128/115 | 37/342 | 373/121 | SCC | 0.5 |
| Lovatt (2005) | Caucasian | UK | 509/379 | 224/216 | 69/151 | 163/65 | BCC | 0.19 |
| Debniak (2006) | Caucasian | Poland | 425/1262 | 168/188 | 69/492 | 597/173 | melanoma | 0.93 |
| Li (2006) | Caucasian | USA | 602/603 | 242/290 | 70/273 | 259/71 | melanoma | 0.73 |
| Millikan (2006) | Caucasian | USA | 1176/2397 | 1039/1098 | 162/1039 | 1098/260 | melanoma | 0.49 |
In subgroup analysis, we found that the Asp312Asn polymorphism was not linked to increased risk of cutaneous melanoma, nonmelanoma skin cancer or basal cell carcinoma.

Sensitivity analyses were performed after the sequential removal of each eligible study to assess the influence of each individual study on the pooled OR. The result of sensitivity analyses showed that any single study could not change the pooled ORs qualitatively, indicating robustness and reliability of our results.

Publication bias

Begg’s funnel plots were created to evaluate the potential publication bias. The shapes of Begg’s funnel plots did not reveal any evidence of obvious asymmetry.
Discussion

The damages of DNA resulted from various environmental factors, such as radiation, diet and smoking. Unrepaired DNA gives rise to gene mutations, chromosomal alterations, and genomic instability, which may activate carcinogenesis finally. DNA repair pathways play a crucial part in the removal of damages, repair of base alterations caused by UVR, recombination of homologous or nonhomologous end joining, and other injuries caused by many carcinogenic agents (Yu et al., 1999; Wood et al., 2001). The NER pathway is one of the most important DNA repair pathways, which removes bulky adducts, such as those caused by environmental agents, UVR induced DNA damage, crosslinks and oxidative damage (Sancar et al., 1993; Weeda et al., 1993).

XPD gene, located at chromosome 19q13.3, comprises 23 exons and spans about 54,000 base pairs (Lamerdin et al., 1996). It encodes an evolutionarily conserved ATP-dependent DNA helicase protein, a basal transcription initiation factor complex TFIIH, which is essential for NER (Weber et al., 1988), basal transcription, and apoptosis (Wang et al., 1996). The XPD gene is involved in the DNA helix opening, and is capable of removing helix-distorting base lesions produced by ultraviolet light and chemical agents (Lehmann et al., 2001). The XPD 751Gln and 312Asn variants substantially alter the amino-acid electronic configuration in a domain important for the interaction with the helicase activator p44 and may change the function of XPD (Coin et al., 1998). Benhamou S et al. have demonstrated that XPD Lys751Gln and Asp312Asn polymorphisms were associated with lower DNA repair capacity and a higher level of DNA adducts, which might be susceptible to cancer (Benhamou et al., 2002).

There are increasing interests in exploring the associations between the XPD Lys751Gln and/or Asp312Asn polymorphisms and susceptibility or resistance to cancer development. However, results remain conflicting rather than conclusive, which impelled researchers to pay attention to these two polymorphisms at a meta-analytical level. On the whole, three newly updated meta-analyses revealed that there were no evidence supporting that XPD Lys751Gln polymorphism contributed to prostate cancer (Ma et al., 2013), colorectal cancer (Zhang et al., 2011), or gastric cancer (Yin et al., 2013). On the contrary, other large sample meta-analyses proposed a greater risk in hepatocellular carcinoma (Guo et al., 2012), breast cancer (Yan et al., 2014), lung cancer (Li et al., 2014), glioma (Chen et al., 2012), and acute myeloid leukemia (AML) (Liu et al., 2014). For XPD Asp312Asn polymorphism, three meta-analyses proposed a greater risk in prostate cancer (Ma et al., 2013), gastric cancer (Yin et al., 2013), and esophageal cancer (Duan et al., 2012). However, other large sample meta-analyses showed that it did not contribute to breast cancer (Yan et al., 2014), lung cancer (Li et al., 2014), colorectal cancer (Zhang et al., 2011) or head and neck cancer (Hu et al., 2012) risk.

In reference to skin cancer susceptibility, the first study considering XPD Lys751Gln polymorphism as a potential molecular marker was performed by Dybdahl et al. in 1999 (Dybdahl et al., 1999), which investigated 40 cases and 40 controls. It showed that subjects carrying two A alleles (AA genotype) were at 4.3-fold higher risk of BCC than subjects with two C alleles, suggesting the variant C-allele may be protective. Nonetheless, Winsey et al. (Winsey et al., 2000) reported that XPD Lys751Gln polymorphism was not related to the risk of cutaneous melanoma. Winsey et al. (Winsey et al., 2000) firstly reported the association between Asp312Asn polymorphism and skin cancer risk, and also, Asp312Asn polymorphism was not linked to susceptibility to cutaneous melanoma. Until now, a large amount of studies have been published to investigate the associations of XPD Lys751Gln or Asp312Asn polymorphisms with skin cancer susceptibility. Nevertheless, the results are poorly understood.

To further clarify the relationship between XPD Lys751Gln and/or Asp312Asn polymorphisms and skin cancer risk, we performed this meta-analysis. Our results suggested that XPD Lys751Gln polymorphism was not linked to increased risk of skin cancer. Subgroup analysis based on tumor type indicated the XPD Lys751Gln polymorphism was not associated with increased risk of nonmelanoma skin cancer, but significantly associated with increased risk of cutaneous melanoma (Gln/Gln vs. Lys/Lys: OR=1.15, 95%CI=1.02-1.29, P=0.023; dominant model: OR=1.09, 95%CI=1.01-1.18, P=0.036). Nevertheless, the pooled ORs indicated that Asp312Asn polymorphism was associated with neither overall nor stratified skin cancer in all genetic models.

When conducting meta-analysis, heterogeneity is one of the important issues. Although we minimized the likelihood by performing a careful search for published studies, using the explicit criteria for study inclusion,
statistical significant heterogeneity still existed in three comparisons (dominant model for Lys751Gln polymorphism: I²=34.6, P=0.080; Asn/Asn vs. Asp/Asp for Asp312Asn polymorphism: I²=46.7, P=0.050; and recessive model for Asp312Asn polymorphism: I²=52.9, P=0.024). After subgroup analysis by tumor type, the heterogeneity was effectively reduced or removed, suggesting that certain effects of genetic variants are tumor type-specific. The results of sensitivity analyses showed no single study exhibited excessive influence, suggesting that the results of this meta-analysis were relatively stable. In addition, Begg’s funnel plots and Begg’s tests did not detect any publication bias and our results were unbiased.

Several limitations of this meta-analysis should be acknowledged when considering its contributions. First of all, the sample size of squamous cell carcinoma was relatively small. Thus, we do not have enough data to confirm the relationship between XPD polymorphisms with squamous cell carcinoma risk. Secondly, our meta-analysis’s results were only applicable to Caucasians, and there was no relevant study from Asians or Africans. Hence, to evaluate the effect of XPD Lys751Gln and Asp312Asn polymorphisms on skin cancer risk, additional studies involving different ethnicities are needed. Thirdly, subgroup analyses based on environmental exposure were not performed on account of the insufficient data. Finally, gene-environment interactions were also not explored in this meta-analysis.

In summary, our meta-analysis suggests that XPD Lys751Gln polymorphism may contribute to the risk of cutaneous melanoma from currently available evidence. Considering the limited sample size and ethnicities included in the meta-analysis, larger and well-designed studies are required to confirm these findings. Moreover, future studies should evaluate gene-environment interactions to identify the role of the XPD polymorphisms in skin cancer.

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XPD Lys751Gln and Asp312Asn Polymorphisms and Susceptibility to Skin Cancer: a Meta-analysis

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