**XRCC1 and XPD genetic polymorphisms and susceptibility to age-related cataract: A meta-analysis**

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**Objective:** This meta-analysis aimed to determine the relationships between XRCC1 Arg399Gln (rs25487 G>A) and XPD Lys751Gln (rs1052559 A>C) polymorphisms and susceptibility to age-related cataract.

**Methods:** Medline (1966–2013), the Cochrane Library Database (Issue 12, 2013), EMBASE (1980–2013), CINAHL (1982–2013), Web of Science (1945–2013) and the Chinese Biomedical Database (CBM; 1982–2013) were searched without language restrictions. Various combinations of the keywords and MeSH terms were used to screen for potentially relevant studies, specifically "genetic polymorphisms" or "SNPs" or "variation" or "single nucleotide polymorphism" or "polymorphism" or "mutation" or "variant"; "X-ray repair cross complementing protein 1" or "Xeroderma Pigmentosum Group D Protein" or "X-ray repair cross complementing protein 1" or "Xeroderma Pigmentosum Group D Protein" or "XPD" or "Xeroderma Pigmentosum Complementation Group D Protein" or "ERCC2" or "XRCCI" or "XRCC1 DNA repair protein"; and "Cataract" or "Membranous Cataract" or "Pseudoephakia." Meta-analyses were conducted using Stata 12.0 software. Crude odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI) were calculated.

**Results:** Six independent case-control studies were included in the meta-analysis. Our results indicated that the association between the genetic polymorphisms of XRCC1 Arg399Gln G>A and XPD Lys751Gln A>C and increased susceptibility to age-related cataracts was statistically significant (XRCC1 Arg399Gln: OR=1.30, 95% CI=1.17–1.44, \(p<0.001\); XPD Lys751Gln: OR=1.25, 95% CI=1.12–1.40, \(p<0.001\), respectively). Ethnicity-stratified analysis indicated that the XRCC1 Arg399Gln G>A polymorphism was correlated with the development and progression of age-related cataract in China, India, and Turkey in the allele model and the dominant model. For the XPD Lys751Gln A>C variant, the association with the pathogenesis of age-related cataract in China and Turkey in the allele model and the dominant model was investigated.

**Conclusions:** The association of XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms with age-related cataract susceptibility observed in our meta-analyses supports the view that XRCC1 and XPD may play important roles in susceptibility to age-related cataract.

Age-related cataract is a serious eye disease characterized by the loss of lens transparency and lens protein damage [1]. It is estimated that age-related cataracts are the leading cause of visual impairment and blindness in the elderly population worldwide [2]. According to a World Health Organization report, in 2010, approximately 20 million people worldwide have been reported to suffer from cataracts accounting for about 51% of all cases of blindness [3]. In addition, due to the rapid growth of the aging population, the prevalence and incidence of age-related cataracts have increased in recent years, and most new cases of cataracts are from low- and middle-income countries [4]. A complex and multifactorial disease, age-related cataract may be caused by the interaction between genetic and environmental factors, although the etiology of age-related cataracts is not clearly known [5-7]. Various environmental risk factors, such as diabetes, hypertension, sunlight or exposure to ultraviolet (UV) light, toxins, tobacco smoking, vitamin E deficiency, and body mass index, may contribute to the development and progress of age-related cataracts [8-11]. Calpain proteolysis of fodrin is also suggested to be a critical event in lens damage during the process of cataract development [12]. In recent years, a growing number of reports have focused on the association between certain related genes that may cause the lens proteins to denature and increase susceptibility to age-related cataracts [13,14].

The human X-ray cross-complementing group 1 (XRCC1) is the most well-known DNA repair protein, complexing with at least three different enzymes, poly-ADP-ribose polymerase (PARP), DNA ligase III, and DNA polymerase β [15]. The human XRCC1 gene (Gene ID 37414; OMIM 21171001 and 21174504) is 33 kb long and located on chromosome 19q13.2–13.3, consists of 17 exons, and encodes a 2.2 kb transcript, which corresponds to a putative protein...
of 633 amino acids [16,17]. Evidence has shown that XRCC1 is implicated in single-strand breaks (SSBs) and the base excision repair (BER) pathway and has been reported to be responsible for the efficient repair of DNA damage caused by ionization, oxygen, and alkylating agents [18,19]. Several polymorphisms were investigated in the XRCC1 gene with the coding polymorphism resulting in amino acid substitutions detected at codon 399 (Arg-Gln) receiving the most attention [20,21]. Previous studies documented that the SNPs of XRCC1 may have a strong association with the ability to repair NDA; they could potentially influence many age-related diseases including cancers, atherosclerosis, and eye problems such as glaucoma, age-related macular degeneration, and pterygium [22-25]. More importantly, genetic polymorphisms of XRCC1 have also been frequently documented in many human age-related cataract cases [14,26]. In this regard, we hypothesize that the genetic polymorphisms of XRCC1 may be related to the development and progression of age-related cataract. The polymorphisms of the XRCC1 gene codon Arg399Gln result from a guanine to adenine nucleotide substitution occurring in the PARP binding domain, which may affect the efficiency of complex assembly or repairs and consequently be correlated with susceptibility to age-related cataracts [27].

Epidemiological studies have shown that DNA repair enzymes consecutively provide surveillance on chromosomes that may correct damaged nucleotide residues generated by exposure to carcinogens or cytotoxic compounds. Thus, other DNA repair enzymes may be essential in the pathogenesis of age-related cataracts [28]. Xeroderma pigmentosum complementation group D (XPD) is another DNA repair protein belonging to the RAD3/XPD subfamily of helicases [29]. XPD is suggested to participate in the nucleotide excision repair (NER) pathway and basal transcription as part of the transcription factor IIH [30]. The XPD gene (Gene ID 7515; OMIM 43543312 and 43575578) maps to chromosome 19q13.3 and contains 22 exons and 21 introns spanning approximately

Figure 1. Flowchart of the literature search and study selection. Six case-control studies were included in the meta-analysis.
2.3 kb [31]. Since XPD is critical in the tasks of multiple cells and XPD mutations have been investigated in the pathogenesis of many genetic diseases, XPD genetic polymorphisms may therefore be accepted as a key genetic susceptibility factor [32]. Currently, some SNPs in the XPD gene’s exons have been identified, with the Lys751Gln polymorphism the most common [33,34]. The Lys751Gln polymorphism may contribute to the production of the most relevant change in XPD function and may have an impact on DNA repair capacity, thus connecting it to age-related cataract susceptibility [35]. Recently, several studies have shed further light on the possibility that XRCC1 and XPD genetic polymorphisms may be correlated with age-related cataract susceptibility [35,36]. However, studies thus far have not shown a consistent link [14,26]. In view of this shortcoming, we conducted this meta-analysis to provide more solid evidence and minimize the potential bias caused by limited publications in the past. In this study, we performed a meta-analysis of all available case-control studies to summarize the relationships of the most widely studied XRCC1 and XPD genetic polymorphisms with susceptibility to age-related cataracts.

METHODS

Literature search: Studies addressing the correlation of XRCC1 and XPD genetic polymorphisms with susceptibility to age-related cataracts were identified by searching for articles in the following electronic databases: Medline (1966–2013), the Cochrane Library (Issue 12, 2013), EMBASE (1980–2013), PubMed (1966–2013), CINAHL (1982–2013), Web of Science (1945–2013), and Chinese Biomedical (CBM; 1982–2013). Various combinations of keywords and MeSH terms were used to screen for potentially relevant studies, specifically “genetic polymorphisms” or “SNPs” or “variation” or “single nucleotide polymorphism” or “polymorphism” or “mutation” or “variant”; “X-ray repair cross complementing protein 1” or “Xeroderma Pigmentosum Group D Protein” or “X-ray repair cross complementing protein 1” or “Xeroderma Pigmentosum Group D Protein” or “XPD” or “Xeroderma Pigmentosum Complementation Group D Protein” or “ERCC2” or “XRCCI” or “XRCCI DNA repair protein”; and “Cataract” or “Membranous Cataract” or “Pseudoaphakia.” A manual search using the basis of references identified in the included articles was also performed to obtain other potential articles.

Inclusion and exclusion criteria: The eligible studies included in our meta-analysis should meet the following three inclusion criteria: (1) It is a clinical cohort study focused on the relationships between XRCCI Arg399Gln (rs25487 G>A) and XPD Lys751Gln (rs1052559 A>C) polymorphisms and age-related cataract susceptibility. (2) All patients must conform to the diagnostic criteria of age-related cataracts, and the differentiation method of the degree of turbidity of lenses from patients with cataracts were as follows: Chylack’s Lens Opacities Classification System (LOCS) or Sasaki’s EAS-1000 Scheimpflug method [12,37]. (3) Enough information about the polymorphisms of XRCCI Arg399Gln (rs25487 G>A) and XPD Lys751Gln (rs1052559 A>C) should be supplied in all eligible articles. Exclusion criteria were the following: (1) letters, reviews, case reports, conference abstracts, editorials, and expert opinions; (2) studies in
| First author | Year | Country | Disease | Number | Gender (M/F) | Age (year) | Genotyping method | Gene | SNP | NOS score |
|--------------|------|---------|---------|--------|--------------|------------|-------------------|------|-----|-----------|
| Xu HF [38]   | 2013 | China   | Senile cataract | 260 | 269 | - - | 67.0±10.6 | 68.8±10.5 | Direct sequencing | XPD | Lys751Gln A>C | 6 |
| Guo MJ [34]  | 2013 | China   | Senile cataract | 260 | 276 | - - | 67.0±11.0 | 68.8±10.5 | Direct sequencing | XRCC1 | Arg399Gln G>A | 6 |
| Zhang Y [24] | 2012 | China   | Cortical | 415 | 386 | 220/195 | 202/184 | 67.17±6.9 | 65.8±6.5 | PCR-RFLP | XRCC1 | Arg399Gln G>A | 8 |
| Padma G [12] | 2011 | India   | Senile cataract | 208 | 151 | 91/117 | 94/57 | 58.6±0.4 | 49.1±0.6 | PCR-RFLP | XRCC1 | Arg399Gln G>A | 8 |
| Luo YF [33]  | 2011 | China   | Senile cataract | 180 | 174 | 65/115 | 61/113 | 68.0±8.0 | 61.5±7.0 | PCR-RFLP | XPD | Lys751Gln A>C | 7 |
| Unal M [25]  | 2007 | Turkey  | Cortical / Cortical / Posterior subcapsular / Mixed | 195 | 194 | 99/96 | 105/89 | 64.0±8.0 | 63.0±8.0 | PCR-RFLP | XRCC1 | Arg399Gln G>A | 8 |

M=male; F=female; NOS=Newcastle-Ottawa Scale criteria; PCR-RFLP=polymerase chain reaction-restriction fragment length polymorphism; SNP=single nucleotide polymorphism.
languages other than English or Chinese; and (3) studies on polymorphisms other than the selected two. Additionally, if the eligible study was reported in duplication, the latest article published in English or the study with the largest sample size was included in this study.

Data extraction and methodological assessment: Two authors (Duo Ba and Su-Ning Shi) used a standardized form to systematically collect relevant data. For all studies, we extracted the following data from the original publications: the first author, the publication year of the article, the language of the publication, the geographical location, the design of the study, the total number and mean ages of the cases and controls, the sample size, the source of the subjects, the method for detecting genotypes, and the distribution of the genotypes.

Methodological quality was separately assessed by two observers using the Newcastle-Ottawa Scale (NOS) criteria [38]. The NOS criteria consisted of three aspects: (1) subject selection: 0–4; (2) comparability of subjects: 0–2; and (3) clinical outcome: 0–3. The NOS scores ranged from 0 to 9 with a good quality score ≥7.

Statistical analysis: For rigorous statistical analysis, we chose Stata statistical software (version 12.0, Stata Corporation, College Station, TX) to deal with statistical data. The relationships between genetic polymorphisms and age-related cataracts were estimated with odds ratios (OR) and the corresponding 95% confidence interval (95% CI). The statistical significance of the pooled ORs was evaluated with the Z test. The possibility of heterogeneity between studies was assessed with Cochrane's $Q$-statistic and $I^2$ tests [39]. A p value <0.05 or $I^2 >50\%$ meant that these studies were heterogeneous, and thus, the random-effect model was used. Otherwise, the fixed-effects model was implemented. Stratified analyses were conducted for host ethnicity and disease base. Further sensitivity analyses were conducted to investigate the potential origin of the heterogeneity. Potential publication bias was

Figure 3. Forest plots for the relationships of $XRCC1$ and $XPD$ SNPs with susceptibility to age-related cataract under the allele and dominant models.
also investigated with the use of funnel plots and Egger’s linear regression test [40].

**RESULTS**

Characteristics of the included studies: Initially, our highly sensitive search strategy identified 23 articles. We reviewed

![Figure 4. Subgroup analyses for the relationships of XRCCI and XPD SNPs with susceptibility to age-related cataract under the allele and dominant models.](http://www.molvis.org/molvis/v21/335/)}
the titles and abstracts of all articles and excluded seven. Then we systematically reviewed their full texts and excluded six articles. Another two studies were also excluded due to the lack of data integrity (Figure 1). Ultimately, six clinical case-control studies met our inclusion criteria for quantitative data analysis [14,26,27,35,36,41]. The publication years of the eligible studies ranged from 2007 to 2013. The distribution of the number of topic-related works in the electronic database during the last decade is shown in Figure 2. As shown in Table 1, among the included articles, all six studies were conducted among Asian populations (four in China, one in India, and one in Turkey). The classic polymerase chain reaction-amplified genes with restriction endonucleases (PCR-RFLP) method was used in four studies while the other two studies used the direct sequencing method. Two common polymorphisms (XRCC1 Arg399Gln and XPD Lys751Gln) were assessed. The genotype frequencies of the controls were all in Hardy–Weinberg equilibrium (HWE; all p>0.05). The NOS scores for all included studies were ≥6 (moderate-high quality). We summarize the baseline characteristics and methodological quality in Table 1.

Quantitative data synthesis: The meta-analysis results showed that genetic polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln have statistically significant associations with increased susceptibility to age-related cataracts (XRCC1 Arg399Gln: allele model: OR=1.30, 95% CI=1.17–1.44, p<0.001; dominant model: OR=1.38, 95% CI=1.21–1.56, p<0.001; XPD Lys751Gln: allele model: OR=1.25, 95% CI=1.17–1.34, p<0.001).

Figure 5. Sensitivity analysis of the summary odds ratio coefficients on the relationships of XRCC1 and XPD SNPs with susceptibility to age-related cataract under the allele and dominant models.
CI=1.12–1.40, p<0.001; dominant model: OR=1.34, 95% CI=1.16–1.54, p<0.001; Figure 3).

We also conducted subgroup analysis to investigate the potential influence of factors on individuals’ risk of age-related cataracts. In the subgroup analysis based on country, we found that the XRCC1 Arg399Gln G>A polymorphisms were correlated with development and susceptibility to age-related cataracts among residents of China, India, and Turkey in the allele model (all p<0.05) and among China and India in the dominant model (all p<0.05). For the XPD Lys751Gln A>C polymorphism, the association with the pathogenesis of age-related cataracts among Turkey in the allele model (OR=1.48, 95% CI=1.23–1.78, p=0.001) and among China and Turkey in the dominant model (China: OR=33.37, 95% CI=20.93–53.21, p<0.001; Turkey: OR=5.70, 95% CI=3.43–9.47, p<0.001) was investigated (Figure 4). Furthermore, in the disease subgroup analysis, there were significant connections between the XRCC1 Arg399Gln polymorphism and the risk of mixed and nuclear cataracts in Turkey (mixed: allele model: OR=1.36, 95% CI=1.13–1.64, p=0.001; dominant model: OR=1.44, 95% CI=1.16–1.79, p=0.001; nuclear: allele model: OR=1.35, 95% CI=1.06–1.69, p=0.008; dominant model: OR=1.45, 95% CI=1.07–1.97, p=0.016), but no such relation was observed in the cortical and posterior subcapsular cataract groups (cortical: allele model: OR=1.23, 95% CI=0.99–1.54, p=0.064; dominant model: OR=1.31, 95% CI=0.92–1.85, p=0.134; posterior subcapsular: allele model: OR=1.14, 95% CI=0.88–1.48, p=0.313; dominant model: OR=1.21, 95% CI=0.86–1.71, p=0.282). We also found that polymorphisms of XPD Lys751Gln were related to the risk of mixed cataracts in the allele model (OR=1.20, 95% CI=1.03–1.39, p=0.016) and mixed cataract, cortical, nuclear, and posterior subcapsular cataract in the dominant model (mixed cataract: OR=26.26, 95% CI=9.42–73.22, p<0.001;...
in accordance with a previous study suggesting that significant changes in the DNA repair of glutamine for arginine at codon 399, eventually leading to polymorphism in the genesis of age-related cataracts. Specifically, the Arg399Gln polymorphisms may be a critical event related to the patho-
tive radiation and inflammatory DNA damaging processes single-strand DNA breaks resulting from endogenous oxid-
ization between the development of lens opacities and oxidative stress or UV light-induced DNA damage in the lens epithe-
lyum has been reported, and the effects of DNA repair in lens epithelial cells have also been proved. Although the XRCC1 gene codes for one of the major DNA repair proteins, the exact mechanisms that the XRCC1 genetic polymorphisms play in the progression of age-related cataracts are still unclear. It is noteworthy that XRCC1 was demonstrated to be implicated in single-strand breaks and the BER pathway, which is one of the most important pathways involved in the repair of oxidative and UV-related DNA damage [44].

Sensitivity analysis indicated that a single study could not have an influence on the overall pooled ORs (Figure 5). Our results showed no apparent evidence of asymmetry in the funnel plots, and no publication bias was found in Egger’s test (all p>0.05; Figure 6).

**DISCUSSION**

Much research effort has been directed toward understanding the role of genetic polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln in susceptibility to age-related cataracts. Our results indicated that the XRCC1 Arg399Gln polymorphism was related to increased susceptibility to age-related cata-
racts. It is widely accepted that the loss of lens transparency is a common pathological abnormality synonymous with cataracts due to the lens fiber cells not having any nuclei to induce the proteins involved in DNA repair [42]. An association between the development of lens opacities and oxidative stress or UV light-induced DNA damage in the lens epithelium has been reported, and the effects of DNA repair in lens epithelial cells have also been proved [43]. Although the XRCC1 gene codes for one of the major DNA repair proteins, the exact mechanisms that the XRCC1 genetic polymorphisms play in the progression of age-related cataracts are still unclear. It is noteworthy that XRCC1 was demonstrated to be implicated in single-strand breaks and the BER pathway, which is one of the most important pathways involved in the repair of oxidative and UV-related DNA damage [44].

Specifically, oxidative stress is involved in cataractogenesis; in this regard, the role of antioxidants could be considered as a potential cataract preventive agent [45,46]. A potential explanation is that the active oxygen radicals damage the lens epithelial cells, and large conformational changes in proteins may be found as protein–protein cross-links, which causes a corresponding increase in concentration [42]. It is hinted that the use of antioxidants can be of great importance in preventing cataracts. However, the variants of XRCC1 may contribute to disturbing single-base damage repair and single-strand DNA breaks resulting from endogenous oxidative radiation and inflammatory DNA damaging processes [35]. In this regard, our findings suggest that XRCC1 genetic polymorphisms may be a critical event related to the patho-
genesis of age-related cataracts. Specifically, the Arg399Gln polymorphism in the XRCC1 gene may result in a substitution of glutamine for arginine at codon 399, eventually leading to significant changes in the DNA repair [27]. Our findings are in accordance with a previous study suggesting that XRCC1 genetic polymorphisms may be an alternative mechanism of gene silencing in BC cell lines and primary breast carcinomas [35]. Our meta-analysis also indicated that the XPD polymor-
phisms also play a critical role in the elevated susceptibility to age-related cataracts and the XPD Lys751Gln A>C polymorphism in particular, revealing that this mutation was also regarded as one of the potential mechanisms increasing the risk of age-related cataracts. In fact, XPD is suggested to be involved in the NER repair pathway and basal transcription as part of the transcription factor IIH [30]. In addition, the NER pathway usually participates in the repair of bulky and helix-distorting adducts induced by chemical carcinogens and radiation [47]. Nevertheless, certain genetic mutations in the XPD gene may result in the production of the most relevant change in XPD function and may influence DNA repair capacity, and thus could have an adverse impact on the development of age-related cataracts [27]. Moreover, the XPD Lys751Gln polymorphism is an adenine (A) to cytosine (C) transition, which may cause the change from lysine to glutamine in exon 23 of the XPD gene, and consequently have a negative role in the DNA repair effect [48]. Consistent with our results, Padma and colleagues also concluded that the XPD genetic polymorphism was associated with the development of maturity-onset cataract [14].

We also performed this subgroup analysis based on ethnicity; the results indicated that there was a significant relationship between the genetic polymorphisms of XRCC1 Arg399Gln G>A and the risk of age-related cataracts, but an association was also observed in the XPD Lys751Gln A>C polymorphism in China and Turkey, revealing that there was no difference related to ethnicity in the relationship of XRCC1 Arg399Gln and XPD Lys751Gln with the risk of age-related cataract. In short, this meta-analysis supports the conclusion that the genetic polymorphisms of XRCC1 Arg399Gln G>A and XPD Lys751Gln A>C may lead to the progression of age-
related cataracts, suggesting that XRCC1 and XPD genetic polymorphisms may be useful as biomarkers in the early detection of clinical age-related cataracts.

The limitations in this systematic meta-analysis should be kept in mind. First, the potential confounding effect of sex, disease, and ethnicity was not controlled for in large parts of the included studies, which limits the explanatory power of our findings and the subsequent subgroup analyses. Second, due to the small number of studies, our results did not include data from all trials that evaluated the relationships of XRCC1 and XPD genetic polymorphisms with the pathogenesis of age-related cataract. A third limitation of our meta-analysis is the crude division criteria of ethnic groups into “Caucasian,” “Asian,” or “African,” making the research
prone to bias whereas our analyses focused on the Asian populations. Further studies from different populations are necessary to clarify the present results. We restricted publications to those published in English or Chinese, which may be related to the possible bias in our data analyses as well. Another limitation might be that our meta-analysis may still be underpowered due to our inability to acquire the original data from the existing included studies. In addition, although no significant evidence of publication bias was found in the Egger test, positive results were prone to be accepted by reviewers and editors; this initially restricted our research on this topic and may result in the occurrence of publication bias. Despite the previous limitations, this is the first meta-analysis of the associations of XRCC1 and XPD genetic polymorphisms with age-related cataract. More importantly, our meta-analysis used a statistical approach to combine the results from multiple studies. We rigorously quantified and analyzed the inconsistent results in our meta-analysis, leading to a more reliable conclusion.

In conclusion, our meta-analysis indicates that XRCC1 and XPD genetic polymorphisms may be associated with age-related cataract risk. Thus, XRCC1 and XPD genetic polymorphisms may be useful for identifying age-related cataract patients at an early stage. Larger, well-designed case-control studies with subjects of the same ethnic background and tissue-specific biochemical and biologic characterizations are required to validate these findings. Additionally, further studies of the precise mechanisms by which genetic polymorphisms of DNA repair genes influence the history of cataract progression are necessary.

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