Meta-analysis of Genetic Polymorphisms and Ophthalmologic Disease Risk in Asian Populations: a Case of DNA Repair XRCC1 Gene

1Najmaldin Saki, 2Hamid Gafkhari, 3Mostafa Feghhi, 4Fatemeh Ardehish Larijani and 5Fakher Rahim
1Cellular and Molecular Research Center, Department of Hematology and Oncology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Tarbiat Modares University, Tehran, Iran
2Department of Genetic, Faculty of Science, Shahid Chamran University, Ahvaz, Iran
3Department of Ophthalmology, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran
4Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Ahvaz, Iran
5Toxicology Research Center, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran

Abstract: This study aimed to assess a meta-analysis of the association of XRCC1 polymorphisms with the risk of various ophthalmologic diseases in Asian population. This meta-analysis was performed by critically reviewing reveals 38 studies involving 1373 cases and 1745 controls. Among all the eligible studies, one focused on Arg194Trp polymorphism, nine described the Arg399Gln and no article investigated on Arg280His. There was a large between-study heterogeneity in ORs of individual studies of the dominant model ($\chi^2 = 74.18, I^2 = 58.9\%$, $p = 0.013$) and the additive ($\chi^2 = 56.18, I^2 = 41.4\%$, $p = 0.091$) models, but a moderate heterogeneity in the recessive model ($\chi^2 = 72.27, I^2 = 78.8\%$, $p = 0.000$) was observed. So, we pooled the results using the random-effect analysis and found that Arg399Gln has a weak relation with ophthalmologic disease in the recessive ($OR = 0.96, 95\% CI: 0.64-1.44$), the dominant ($OR = 1.05, 95\% CI: 0.82-1.33$) and the additive ($OR = 1.15, 95\% CI: 0.77-1.70$) models and the meta-analysis correspondingly shows that comprising diverse population is very important since susceptibility loci might vary indifferent ethnic groups. To ratify our findings, widespread studies with enlarged sample size and various populations are essential to explain the role of all polymorphism of XRCC1 genes in the pathogenesis of ophthalmologic diseases. Finally, our meta-analysis showed Arg399Gln variant was not associated with increased ophthalmologic diseases risk via dominant and recessive modes among Asian population.

Key words: XRCC1 gene, polymorphisms, Arg194Trp, Arg399Gln, ophthalmologic diseases, ethnicity

INTRODUCTION

There is increasing evidence suggests that damage to human DNA might initiate the cancer, which caused by external agents such as chemical agents, ionizing radiation and UV (Carpenter et al., 1998; Okayasu, 2012; Rastogi et al., 2010; Yanez et al., 2002). The X-ray repair cross-complementing group 1 (XRCC1) is a DNA repair gene and a number of its single nucleotide polymorphisms (SNPs) have been considered as a modifying risk factor for variety of cancer types. Three different polymorphisms in XRCC1 gene have been identified at codon 399 (Arg to Gln), 194 (Arg to Trp) and 280 (Arg to His) up to now (Shen et al., 1998), which were predicted to be possibly damaging the XRCC1 function (Metsola et al., 2005). The interactions of XRCC1 and its substrate result in assembly of the repair complex at the site of damage and regulate the activity of several repair enzymes (Caldecott et al., 1996). The polymorphism Arg399Gln changes XRCC1’s structure and maybe disrupt the combination of several repair enzymes, particularly poly (ADP-ribose) polymerase 1 (PARP1). Arg194Trp and Arg280His also change XRCC1’s structure but maybe not influence the function of XRCC1.

Previous analysis of case-control reports is the most predominant method of exploring the association between a specific gene and a disease. However, studies on XRCC1 polymorphisms in cancer have provided challenging and controversial results so far. Although other studies have found that the XRCC1 increase in cancer risk (Loizidou et al., 2008; Saadat et al., 2008) and reports showed a possible protective effect (Costa et al., 2007), while many studies observed no significant association between these polymorphisms and the cancer

Corresponding Author: Fakher Rahim, Toxicology Research Center, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran Tel: +986113367562
(Thyagarajan et al., 2006). Besides it was reported that XRCC1 gene polymorphism is associated with several cancers including lung, esophageal and prostate cancers, among different population (Hao et al., 2004; Lee et al., 2001, 2002; Misra et al., 2003; Moulan et al., 2003; Van Gils et al., 2002). Moreover, no evidence of any associations between Arg399Gln polymorphism and bladder cancer susceptibility has not shown (Wang et al., 2008), hence other researchers reported that 399 Gln/Gln genotype is associated with a risk of lung cancer among Asians ethnicity (Kiyohara et al., 2006). Although, large numbers of epidemiologic studies have been evaluated the role of XRCC1 polymorphisms on various ophthalmologic diseases, such as liver cirrhosis, Alzheimer, glaucoma, cataract, HIV-1/AIDS, schizophrenia, type 2 diabetes (Attar et al., 2010; Bau et al., 2007; Bazo et al., 2011; Chen et al., 2010; Chiang et al., 2010; Gorgun et al., 2010; Gu et al., 2007; Guven et al., 2007a, b; Kasznicki et al., 2009; Lin et al., 2009; Luo et al., 2011; Padma et al., 2011; Paridjar-Karpuzoglu et al., 2008; Qian et al., 2010; Rossit et al., 2002; Sobti et al., 2009; Sterpone et al., 2009; Ural et al., 2007; Vural et al., 2009; Warchol et al., 2012; Yang et al., 2009; Yousaf et al., 2011; Zhao et al., 2012) and cancers, but no such comprehensive analysis in the field of ophthalmologic disease, is reported so far.

Nevertheless, a meta-analysis of all existing reports will help to create a more convincing result, because some of these studies were based on small sample size, thus, subgroup analysis based on ethnic and other factors may also yield more meaningful results. It is important to perform a quantitative synthesis of the available evidence using more rigorous methods on the amounts of evidence have been accumulated so far. Therefore, we performed a meta-analysis of all eligible case-control studies published to date, to assess the association of XRCC1 polymorphisms with the risk of various ophthalmologic diseases in different Asian population.

MATERIALS AND METHODS

Study selection: Relevant studies were identified in the PubMed, ISI web of science and Scopus using combinations of the search phrases “X-ray cross-complementing group 1”, “polymorphism”, “DNA repair gene” and all possible combination (the last search update on OCT 12, 2012). In addition, all publications in other databases such as IranMedex, SID (Scientific Information Database) were searched. In a total of 383 retrieved relevant references, nine publications were identified to be eligible for the inclusion in the meta-analysis (Fig. 1). These studies had a case-control study design that assessed the association between the XRCC1 Arg194Trp, the Arg399Gln and Arg280His polymorphisms and risk of ophthalmologic diseases using human genomic DNA samples.

Inclusion criteria

Study design: Case-control studies were included in the evaluation, since this study design allows a comparison to be made between the affected individuals and healthy or disease-free ones, which is essential for the meta-analysis model.

Participants: Studies that included patients with any non-tumorigenic or ophthalmologic condition were included in the evaluation.

Exclusion criteria: Studies that were not representative or not case-control were excluded. The studies that showed not enough data for analysis were excluded after contacting corresponding author twice.

Data extraction: Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that appeared to be relevant were obtained where possible and the relevance of each study independently assessed by two reviewers according to the inclusion and exclusion criteria. Two authors (FR and NS) mined data and reached an agreement on all of the eligibility items, including author, journal and year of publication, location of study, selection and characteristics of cases and controls, control source, demographics, ethnicity and genotyping information.

Meta-analysis: The Odds Ratios (OR) of selected ophthalmologic diseases associated with the XRCC1 Arg194Trp, the Arg399Gln and Arg280His polymorphisms were estimated for each study independently. We estimated the risk first for the variant homozygous genotypes, compared with the wild-type homozygous genotypes, assuming recessive and dominant effect models, respectively.

Statistical analysis: We calculated OR and 95% Confidence Intervals (CI) to estimate ophthalmologic diseases risk associated with the XRCC1 polymorphism for each study. Inevitably, studies included in the meta-analysis differed in the variables of interest and thus, any kind of variability among studies may be termed heterogeneity. In meta-analysis, we examined the association between allele Trp of Arg194Trp and the risk of ophthalmologic diseases compare to that of allele Arg, as well as using additive (Trp/Trp vs. Arg/Arg), recessive
(Trp/Trp vs. (Arg/Trp+Arg/Arg)) and dominant (Trp/Trp+Arg/Trp) vs. Arg/Arg) genetic models. The same method was applied to the other polymorphism. We evaluated the deviations from the Hardy-Weinberg equilibrium for the control group in each study by chi-square test using a web-based program (http://www.ihg.gs/i/bin/hw/hw1.pl) for goodness of fit.

In the present study, both Der Simonian and Laird's random-effects method and Mantel-Haenszel's fixed-effects method were used. In the meta-analysis, to evaluate the between-study heterogeneity both chi-square-based Q-statistic and I-squared ($I^2$) tests were performed. Furthermore, according to Venice criteria, for the $I^2$ test included: <25% represents no heterogeneity, 25-50% represents moderate heterogeneity, = 50-75% represents large heterogeneity and >75% represents extreme heterogeneity (Ioannidis et al., 2008). So the heterogeneity was considered significant, if the p-value<0.10 and $I^2$>25, a random-effect model was suitable, otherwise if the p-value = 0.10 and $I^2$ = 25, a fixed-effect model was then used to estimate summary ORs and 95% CIs. Publication bias was assessed by a funnel plot based on the Egger's regression test and a t-test was implemented to determine the significance of the asymmetry. An asymmetric plot suggested possible publication bias (p - 0.05 suggests no bias). All analyses were done using STATA 11.0 software. All the p-values were two-sided.

**RESULTS**

**Eligible studies:** Nine reports focused on the role of any polymorphism of the XRCC1 gene in the ophthalmologic diseases risk were reviewed. Thus the present meta-analysis reveals 9 studies involving 1373 cases and 1745 controls (Table 1). Each sub-population study has treated...
<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Disease type</th>
<th>Age (Mean±SD)</th>
<th>Genotype studied</th>
<th>Method</th>
<th>Population</th>
<th>Design</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yousaf et al. (2011)</td>
<td>Pakistan</td>
<td>Primary open angle glaucoma</td>
<td>41.3±13.7</td>
<td>160/153</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Panjabi Pakistani</td>
<td>Population-based</td>
</tr>
<tr>
<td>Yousaf et al. (2011)</td>
<td>Pakistan</td>
<td>Primary close angle glaucoma</td>
<td>43.6±15.8</td>
<td>163/193</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Panjabi Pakistani</td>
<td>Population-based</td>
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<tr>
<td>Guven et al. (2007a)</td>
<td>Turkey</td>
<td>Glaucoma</td>
<td>61.3±6.9</td>
<td>144/121</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Turkish</td>
<td>Population-based</td>
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<tr>
<td>Luo et al. (2011)</td>
<td>China</td>
<td>Cataract</td>
<td>68±8</td>
<td>180/174</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Chinese</td>
<td>Hospital-based</td>
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<tr>
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<td>Turkey</td>
<td>Cataract</td>
<td>64±8</td>
<td>195/194</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Turkish</td>
<td>Population-based</td>
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<tr>
<td>Padma et al. (2011)</td>
<td>India</td>
<td>Cataract</td>
<td>58±0.40</td>
<td>208/151</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Indian</td>
<td>Hospital-based</td>
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<tr>
<td>Gorgun et al. (2010)</td>
<td>Turkey</td>
<td>Macular degeneration</td>
<td>75±10</td>
<td>120/205</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Turkish</td>
<td>Population-based</td>
</tr>
<tr>
<td>Chiang et al. (2010)</td>
<td>Taiwan</td>
<td>Pterygium</td>
<td>64.6</td>
<td>127/103</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Taiwanese</td>
<td>Hospital-based</td>
</tr>
<tr>
<td>Chen et al. (2010)</td>
<td>Taiwan</td>
<td>Pterygium</td>
<td>57</td>
<td>83/206</td>
<td>Codon 399</td>
<td>PCR-RFLP</td>
<td>Chinese</td>
<td>Hospital-based</td>
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</table>
Fig. 2(a-c): Forest plots of ORs with 95% CI for XRCC1 polymorphisms and risk of Ophthalmologic disease. Recessive model of (a) Arg194Trp (Trp/Trp vs. Arg/Arg), (b) Dominant model (Trp/Trp vs. Arg/Arg+Arg/Trp) and (c) Additive model (Trp/Trp +Arg/Trp vs. Arg/Arg)

as a separate in the analysis. Among all the eligible studies, one focused on Arg194Trp polymorphism, nine described the Arg399Gln and no article investigated on Arg280His.

**Arg399Gln:** We examined the association between Arg399Gln XRCC1 polymorphism and ophthalmologic diseases risk, assuming various inheritance models of the 399Gln allele for each individual study (Table 2). There was a large between-study heterogeneity in ORs of individual studies of the dominant model ($\chi^2 = 74.18, I^2 = 58.9\%$, $p = 0.013$) and the additive ($\chi^2 = 56.18, I^2 = 41.4\%, p = 0.091$) models, but a moderate heterogeneity in the recessive ($\chi^2 = 72.27, I^2 = 78.8\%, p = 0.000$) was observed. So we pooled the results using the random-effect analysis and found that Arg399Gln has a weak relation with ophthalmologic disease in the recessive (OR = 0.96, 95% CI: 0.64-1.44, Fig. 2A and 3A), the dominant (OR = 1.05, 95% CI: 0.82-1.33, Fig. 2B and 3B) and the additive (OR = 1.15, 95% CI: 0.77-1.70, Fig. 2C and 3C) and models.

**Sensitivity analysis:** We implemented sensitivity analyses to assess the effect of those studies that are not in HWE. The results stayed similar when eliminating those studies. The present analyses of hospital based and population-based studies individually also did not lead to different conclusion. Moreover, meta-regression did not find significant difference between various study designs.

**Publication bias:** Funnel plots and Egger’s test were performed to assess publication bias, which suggested that there were no publication bias for the comparison of Arg399Gln polymorphism, in term of recessive ($t = 1.45, p = 0.19$, Fig. 4A), dominant ($t = -0.1, p = 0.92$, Fig. 4b) and additive ($t = -0.58, p = 0.57$, Fig. 4c) models (Table 3). However, when we stratified Arg399Gln, Arg194Trp polymorphisms, according to different ethnic subgroups include Asian population; there was no public bias in each subgroup (Table 4).

**DISCUSSION**

Large and unbiased molecular and genetic epidemiologic studies of SNPs such as DNA repair genes, may provide insight into the in vitro relations between the candidate genes and ophthalmologic and cancer risk. XRCC1 is very important repair gene for efficient base
<table>
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<tr>
<th>Source</th>
<th>Total</th>
<th>Arg/Arg</th>
<th>Arg/Gln</th>
<th>Gln/Gln</th>
<th>% with Arg allele</th>
<th>Total</th>
<th>Arg/Arg</th>
<th>Arg/Gln</th>
<th>Gln/Gln</th>
<th>% with Arg allele</th>
<th>Matched</th>
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<td>120</td>
<td>98</td>
<td>21</td>
<td>1</td>
<td>90</td>
<td>205</td>
<td>180</td>
<td>25</td>
<td>0</td>
<td>94</td>
<td>Age, sex and ethnicity</td>
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<tr>
<td><strong>Arg399Gln polymorphism</strong></td>
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<tr>
<td>Chiang et al. (2010)</td>
<td>127</td>
<td>9</td>
<td>70</td>
<td>48</td>
<td>65</td>
<td>103</td>
<td>5</td>
<td>31</td>
<td>67</td>
<td>80</td>
<td>Age</td>
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<td>Guven et al. (2007a)</td>
<td>195</td>
<td>65</td>
<td>100</td>
<td>30</td>
<td>59</td>
<td>194</td>
<td>58</td>
<td>115</td>
<td>21</td>
<td>60</td>
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<td>Chen et al. (2010)</td>
<td>83</td>
<td>31</td>
<td>35</td>
<td>17</td>
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<td>104</td>
<td>80</td>
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<td>Padma et al. (2011)</td>
<td>208</td>
<td>90</td>
<td>82</td>
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<td>63</td>
<td>151</td>
<td>75</td>
<td>56</td>
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<td>68</td>
<td>Age and sex</td>
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<td>160</td>
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<td>Younaf et al. (2011)</td>
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<td>79</td>
<td>66</td>
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<td>30</td>
<td>65</td>
<td>98</td>
<td>68</td>
<td>Age and sex</td>
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<td>Luo et al. (2011)</td>
<td>180</td>
<td>13</td>
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<td>14</td>
<td>45</td>
<td>113</td>
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<td>Age and sex</td>
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<td>Guven et al. (2007a)</td>
<td>144</td>
<td>56</td>
<td>78</td>
<td>10</td>
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<td>121</td>
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<td>76</td>
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<td>Age and sex</td>
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<td>Gorgun et al. (2010)</td>
<td>120</td>
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<td>85</td>
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<td>Age, sex and ethnicity</td>
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excision and single-strand break in DNA. The present meta-analysis observed Arg194Trp and Arg399Gln polymorphisms of the XRCC1 gene and their associations with ophthalmologic disease risk in Asian populations and ethnicity, by critically reviewing nine studies.

Many studies indicated the association between the oxidative or UV light DNA damage and cataract development (Kleinman et al., 1990; Pendergrass et al., 2005; Reddy et al., 1998; Risa et al., 2004; Spector, 1995), that the contribution of DNA damage in cataract pathogenesis indicate the role of DNA repair enzymes such as XRCC1. An epidemiologic study that reviewed twenty-two researches revealed a well-documented risk for cataract and DNA damage due to UV exposure (McCarty and Taylor, 2002). Previous studies showed no association between Arg194Trp polymorphism and the indicators of DNA repair capacity, such as, sensitivity to ionizing radiation or DNA-adduct levels (Tuimala et al., 2002, 2004). Our meta-analysis also found evidence that 194Trp variant did not alter the ophthalmologic disease risk among Asian populations. However, other studies showed that this polymorphism exhibited significantly lower values of chromosomal breaks per cell and the protective effect of 194Trp (Patel et al., 2005; Wang et al., 2003). Studies suggest that Arg194Trp polymorphism does not modify the risk for diseases including alcoholic cirrhosis, pre-eclampsia (PE) and idiopathic azoospermia in Asian population (Gu et al., 2007; Qian et al., 2010; Vural et al., 2009), while some studies showed a protective effect against other disease such as Chronic Obstructive Pulmonary Disease (COPD) and pterygium in Asian population (Chiang et al., 2010; Xie et al., 2009). In some meta-analysis about the association between Arg194Trp and risk of cancer considering different genetic models, no evidence of protective effect against bladder and breast cancer has
Fig. 4(a-c): Forest plots of ORs with 95% CI for XRCC1 polymorphisms and risk of Ophthalmologic disease, (a) Recessive model of Arg280His (His/His vs. Arg/Arg), (b) Dominant model (His/His vs. Arg/Arg+Arg/His) and (c) Additive model (His/His+Arg/His vs. Arg/Arg).

Table 3: Egger’s test variables to assess publication bias and comparison of 399Gln vs. 399Arg

<table>
<thead>
<tr>
<th></th>
<th>Recessive</th>
<th>Dominant</th>
<th>Additive</th>
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<tr>
<td>XRCC1 polymorphisms</td>
<td></td>
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<tr>
<td>Genetic models</td>
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<td></td>
<td>t</td>
<td>p-value</td>
<td>t</td>
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<tr>
<td>All diseases</td>
<td>1.45</td>
<td>0.19</td>
<td>-0.1</td>
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<td></td>
<td>-0.58</td>
<td>0.57</td>
<td>-0.58</td>
</tr>
<tr>
<td>*Recessive model of Arg399Gln (Gln/Gln vs. Arg/Arg), Dominant model (Gln/Gln vs. Arg/Arg+Arg/Gln) and (C) Additive model (Gln/Gln+Arg/Gln vs. Arg/Arg)</td>
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Table 4: The association of XRCC1 gene polymorphisms and ophthalmologic risk by assuming different population

<table>
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<tr>
<th>Variables</th>
<th>XRCC1 Polymorphism OR(95%CI)</th>
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<tr>
<td>All diseases</td>
<td>Arg399Gln</td>
</tr>
<tr>
<td>Recessive model</td>
<td>0.96 (0.64-1.44)</td>
</tr>
<tr>
<td>Dominant model</td>
<td>1.04 (0.82-1.33)</td>
</tr>
<tr>
<td>Additive model</td>
<td>1.14 (0.77-1.70)</td>
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been found in Asian and Caucasian (Chen et al., 2011; Huang et al., 2009; Lao et al., 2008; Wang et al., 2008). However, others showed Arg280His genotype increased risk for Differentiated Thyroid Carcinoma (DTC) and Gastric Cardiac Adenocarcinoma (GCA) in dominant model, while mildly reduced the risk for this cancer in Asian population (Fard-Esfahani et al., 2011; Yan et al., 2009). Our meta-analysis also recommends a tendency towards recessive mode of risky effect of 194Trp, which suggest that further studies should be performed to evaluate the effect of this polymorphism.

Moreover, for XRCC1-Arg399Gln polymorphism studies showed that this polymorphism may modify the risk for the ophthalmologic disease including alcoholic cirrhosis, pre-eclampsia (PE), Alzheimer’s disease (AD), ocular diseases include Primary Open Angle Glaucoma (POAG), cataract, Pterygium, severe chronic atrophic gastritis and idiopathic azoospermia in Asian population (Chiang et al., 2010; Gu et al., 2007; Padma et al., 2011; Qian et al., 2010; Rossit et al., 2002; Ural et al., 2007), while some studies showed no association with other disease such as Chronic Obstructive Pulmonary Disease (COPD) and endometriosis in such ethnicity (Attar et al., 2010; Bazo et al., 2011). Several well-known atherosclerotic risk factors, such as dyslipidemia and diabetes mellitus, lead to DNA damage (Andreassi 2003), thus the effects of this risk factors on DNA damage in Coronary Artery Disease (CAD) have been demonstrated formerly (Dincor et al., 2003; Duell et al., 2000) and found no associations between CAD and Arg399Gln
polymorphism in Asian (Turkish) population (Guven et al., 2007a), whereas, other study showed a relationship between CAD and Arg399Gln polymorphisms in Caucasian (Bazo et al., 2011). In Cystic Fibrosis (CF), there was slight correlation between Arg399Gln polymorphism with liver status and pancreatic insufficiency in Caucasian, but this correlation was not significant (Sterpone et al., 2009). In a meta-analysis of Asian (Taiwanese Han Chinese) and Caucasian (Brazilian and Polish) populations showed that the XRCC1 (Arg399Gln polymorphism) was associated with Systemic Lupus Erythematosus (SLE) incidence (Warchol et al., 2012). Furthermore, the XRCC1 (Arg399Gln polymorphism) may affect risk of two major birth defects including spina bifida and oral clefts in Caucasian (USA) population (Olishan et al., 2005). The majority of studies have reported that there was no association between the XRCC1 (codon 399) polymorphism and cancer (Fard-Esfahani et al., 2011; Goode et al., 2002; Huang et al., 2009; Hung et al., 2005; Lao et al., 2008; Yan et al., 2009). In the minority of researches, a weak but statistically significant association has been found in Asian countries, entirely (Garte, 1998; Hu et al., 2005; Kiyohara et al., 2006; Qu and Morimoto, 2005). The present meta-analysis suggests that 399Gln may increases the ophthalmologic disease risk by 30, 25 and 60% with recessive, dominant and additive models in other population only, respectively, which indicated that the genotype distributions of Arg399Gln varied with ethnicity. There may be two explanations concerning the difference in results. Genetic, environmental and ethnic differences in allele frequency for the investigated polymorphisms can affect results in studies. One possible explanation could be the differences in ethnicity in term of dietary habits and drinking, health care access and socioeconomic factors. Another more reasonable clarification may be linked to diversity in linkage or genetic associations between alleles in different populations, which formerly were reported in cancer (Garte, 1998).

CONCLUSION

The present meta-analysis corresponding shows that comprising diverse population is very important since susceptibility loci might vary in different ethnic groups. To ratify our findings, widespread studies with enlarged sample size and various populations are essential to explain the role of all polymorphism of XRCC1 genes in the pathogenesis of ophthalmologic diseases.

Finally, our meta-analysis showed Arg399Gln variant was not associated with increased ophthalmologic diseases risk via dominant and recessive modes among Asian population.

REFERENCES


