Lack of association between three common genetic variations of XPC and susceptibility to age-related macular degeneration, a preliminary study

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Abstract

Background: Numerous association studies have indicated that genetic alterations in genes involved in DNA repair processes are associated with the risk of age-related macular degeneration (ARMD). There is no published study on the relationship between common xeroderma pigmentosum complementation group C (XPC, MIM 613208) polymorphisms and susceptibility to ARMD. The aim of this study is to determine whether three common (Ala499Val, Lys939Gln, and PAT) genetic variants of XPC are associated with the risk of developing ARMD. A total of 120 ARMD patients and 118 healthy controls were included in the study. Genotyping analyses were carried out by PCR-based methods.

Results: Our analysis revealed that there was no relationship between the XPC polymorphisms and susceptibility to ARMD. In both case and control groups, strong linkage disequilibrium existed between three common (Ala499Val, Lys939Gln, and PAT) genetic polymorphisms of XPC. Statistical analysis showed no association between the haplotypes and the risk of ARMD.

Conclusions: The present data indicated that the common polymorphisms of XPC are not susceptible genetic variations for ARMD.

Keywords: DNA repair, Linkage disequilibrium, Macular degeneration, Polymorphism, XPC, Risk

Background

Age-related macular degeneration (ARMD) is a multifactorial complex disease. The photoreceptor degeneration in the central part of the retina leads to the complete loss of central vision. Although the etiology of ARMD is not understood, previous studies have indicated the reactive oxygen species (ROS)-induced damage in ARMD patients [1, 2]. The retina has high level of oxygen consumption. It is revealed that photochemical reactions between light and O₂ lead to the production of ROS [3, 4]. It is well established that ROS can damage cellular macromolecules including DNA. The impaired efficacy of cellular DNA repair might contribute to the pathogenesis of ARMD [5–7].

Xeroderma pigmentosum complementation group C (XPC, MIM 613208) encodes a protein which is involved in nucleotide excision repair by initially detecting the DNA damage [8]. In human populations, the XPC has several common polymorphisms including Ala499Val (rs2228000), Lys939Gln (rs2228001), and PAT [9, 10]. It should be noted that these polymorphisms are associated with cellular DNA repair capacity [11]. Studies have indicated that these polymorphisms are associated with the risk of several multifactorial traits such as cancers [12–15], schizophrenia [16], and dependency to drugs [17].

A meta-analysis of genome wide linkage studies has confirmed that the human chromosome 3p is a
candidate chromosome segment associated with the ARMD [18]. It should be noted that the gene encoding XPC is located on human chromosome 3p25.1 [19]. Previously, the association between common genetic polymorphisms of genes involved in DNA repair processes and susceptibility to ARMD has been reported [20–25]. Taken together, it is concluded that the XPC might be associated with the susceptibility to ARMD. As there is no published study on the association between common XPC polymorphisms and susceptibility to ARMD, this case-control study was carried out.

Methods

This hospital-based case-control study consisted of 120 patients (75 males, 45 females) with exudative ARMD. The patients were recruited from the “Khalili Hospital Ophthalmic clinic” (Fars province, Iran), referred by a vitreoretinal surgeon. Moreover, 118 gender frequency-matched participants (68 males, 50 females) were randomly selected from unrelated volunteers in the same clinic and used as the control group. The mean age (SD) of the ARMD patient and the control groups was 69.6 (9.7) and 63.5 (10.0) years, respectively. There was significant difference in age distribution between the patients and the controls (t = 4.73, df = 236, P < 0.001). Based on the job titles, the participants were categorized into indoor (teachers, housewives, etc.) and outdoor (drivers, farmers, etc.) groups. The outdoor participants were occupationally exposed to sunlight. In the present study, the participants were selected from the same ethnic group (Muslims/Persians) living in Shiraz. This case-control study was approved by the local ethics committee. Informed consent was obtained from all participants.

Genotyping analyses for the Ala499Val (rs2228000) and Lys939Gln (rs2228001) polymorphisms were carried out using specific primers as described previously [9, 10] for the polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLP). The PAT polymorphism is an insertion of 83 bases of A and T [poly (AT)] with a 5-base deletion (GTAAC at position 1457–1461, GenBank Accession No. AF076952) within intron 9 of the XPC gene [26]. Therefore, PCR products of the Ins and Del alleles have different lengths (Fig. 1). Genotyping for this polymorphism was carried out using specific primers as described previously in a simple PCR [10].

For each study polymorphism, the observed genotypic frequencies were compared with the expected frequencies based on the Hardy-Weinberg equilibrium (HWE). Unconditional binary logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for ARMD risk associated with the genotypes of the study polymorphisms. Considering the significant age difference between the cases and the controls, in further analysis, logistic regression was used to estimate ORs and 95% CIs for the various genotypes after adjusting for age. Genetic linkage

| Gender   | Control | Case | χ² (df = 1) | P     |
|----------|---------|------|------------|-------|
| Females  | 50      | 45   | 0.58       | 0.443 |
| Males    | 68      | 75   |            |       |
| Smoking habit |       |      |            |       |
| Non-smoker | 64     | 68   | 5.76       | 0.016 |
| Smoker   | 18      | 42   |            |       |
| Missing  | 36      | 10   |            |       |
| Workplace |         |      |            |       |
| Indoor   | 66      | 66   | 6.21       | 0.013 |
| Outdoor  | 26      | 54   |            |       |
| Missing  | 26      | 0    |            |       |
| Hypertension |     |      |            |       |
| No       | 105     | 112  | 1.03       | 0.309 |
| Yes      | 4       | 8    |            |       |
| Missing  | 9       | 0    |            |       |

| Age       | 63.5 ± 10.0 | 69.9 ± 9.7 | t = 4.76, df = 236 | < 0.001 |
disequilibrium between the alleles of the XPC polymorphisms was estimated using the SNPAlyze (TM) software (ver. 6 Standard, Dynacom Co, Ltd. Kanagawa, Japan). A $P < 0.05$ was considered a statistically significant difference.

**Results**

The general characteristics of the ARMD patients and the control group are summarized in Table 1. In our study subjects, 45.0% (out of 120) of the patients and 28.3% (out of 92) of the healthy controls had outdoor jobs. This difference was statistically significant ($\chi^2 = 6.21, df = 1, P = 0.013$). Among the ARMD patients and the controls, 38.2% (out of 110) and 22.0% (out of 82) were smokers ($\chi^2 = 5.76, df = 1, P = 0.016$), respectively.

Table 2 summarized the genotypic frequency of the three common XPC polymorphisms among the ARMD

| Polymorphisms/genetic models | Controls | Cases | OR  | 95% CI | $P$ | OR* | 95% CI | $P$ |
|------------------------------|----------|-------|-----|--------|-----|-----|--------|-----|
| PAT                          |          |       |     |        |     |     |        |     |
| Additive model               |          |       |     |        |     |     |        |     |
| -/-                          | 33       | 31    | 1.0 | –      | –   | 1.0 | –      | –   |
| -/+                          | 57       | 60    | 1.12| 0.61–2.06| 0.714| 1.11| 0.58–2.11| 0.746|
| +/-                          | 28       | 29    | 1.10| 0.54–2.25| 0.789| 0.92| 0.44–1.95| 0.846|
| Dominant model               |          |       |     |        |     |     |        |     |
| -/-                          | 33       | 31    | 1.0 | –      | –   | 1.0 | –      | –   |
| -/+ and +/-                  | 85       | 89    | 1.11| 0.62–1.97| 0.711| 1.04| 0.57–1.91| 0.881|
| Recessive model              |          |       |     |        |     |     |        |     |
| -/- and -/+                  | 90       | 91    | 1.0 | –      | –   | 1.0 | –      | –   |
| +/-                          | 28       | 29    | 1.02| 0.56–1.85| 0.937| 0.86| 0.46–1.61| 0.653|
| Minor allele frequency       | 0.4788   | 0.4917| 1.05| 0.73–1.50| 0.779|     |        |     |
| Ala499Val                    |          |       |     |        |     |     |        |     |
| Additive model               |          |       |     |        |     |     |        |     |
| Ala/Ala                      | 72       | 73    | 1.0 | –      | –   | 1.0 | –      | –   |
| Ala/Val                      | 41       | 39    | 0.93| 0.54–1.62| 0.819| 1.02| 0.57–1.81| 0.947|
| Val/Val                      | 5        | 8     | 1.57| 0.49–5.05| 0.442| 1.48| 0.45–4.92| 0.515|
| Dominant model               |          |       |     |        |     |     |        |     |
| Ala/Ala                      | 72       | 73    | 1.0 | –      | –   | 1.0 | –      | –   |
| Ala/Val + Val/Val            | 46       | 47    | 1.01| 0.59–1.69| 0.977| 1.07| 0.62–1.86| 0.791|
| Recessive model              |          |       |     |        |     |     |        |     |
| Ala + Ala/Val                | 113      | 112   | 1.0 | –      | –   | 1.0 | –      | –   |
| Val/Val                      | 5        | 8     | 1.61| 0.51–5.08| 0.413| 1.47| 0.45–4.80| 0.517|
| Minor allele frequency       | 0.2161   | 0.2291| 1.07| 0.70–1.66| 0.732|     |        |     |
| Lys939Gln                    |          |       |     |        |     |     |        |     |
| Additive model               |          |       |     |        |     |     |        |     |
| Lys/Lys                      | 31       | 30    | 1.0 | –      | –   | 1.0 | –      | –   |
| Lys/Gln                      | 58       | 61    | 1.08| 0.58–2.01| 0.792| 1.04| 0.54–1.99| 0.899|
| Gln/Gln                      | 29       | 29    | 1.03| 0.50–2.12| 0.929| 0.84| 0.39–1.78| 0.656|
| Dominant model               |          |       |     |        |     |     |        |     |
| Lys/Lys                      | 31       | 30    | 1.0 | –      | –   | 1.0 | –      | –   |
| Lys/Gln + Gln/Gln            | 87       | 90    | 1.06| 0.59–1.91| 0.822| 0.97| 0.52–1.79| 0.927|
| Recessive model              |          |       |     |        |     |     |        |     |
| Lys/Lys + Lys/Gln            | 89       | 91    | 1.0 | –      | –   | 1.0 | –      | –   |
| Gln/Gln                      | 29       | 29    | 0.98| 0.54–1.76| 0.941| 0.82| 0.44–1.52| 0.528|
| Minor allele frequency       | 0.4915   | 0.4958| 1.01| 0.71–1.45| 0.925|     |        |     |

*Adjusted ORs for age of participants
cases and the control subjects. For the Ala499Val, PAT, and Lys939Gln polymorphisms, the minor alleles showed 0.2161, 0.4788, and 0.4915 in the control group, respectively. Our statistical analysis indicated that there was very high similarity between the observed genotypic frequencies and the expected frequencies according to the HWE distribution in the controls (For Ala499Val polymorphism: \( \chi^2 = 0.07, df = 1, P = 0.781 \); For PAT polymorphism: \( \chi^2 = 0.122, df = 1, P = 0.726 \); For Lys939Gln polymorphism: \( \chi^2 = 0.03, df = 1, P = 0.856 \)). Our present data revealed that there was no significant relationship between the XPC polymorphisms and the risk of ARMD (Table 2).

Statistical analysis demonstrated extremely high level of linkage disequilibrium between the XPC polymorphisms (Table 3). The haplotypic frequency in the ARMD cases and the controls are given in Table 4. The frequency of the haplotypes “Ala + Gln,” “Ala – Lys,” “Val – Lys,” and “Ala - Gln” were 113, 69, 51, and 3 in the control group and were 118, 66, 55, and 1 in the ARMD group, respectively. The “Ala + Gln” haplotype was more common compared to the other haplotypes we used as reference group (OR = 1.0). Statistical analysis showed no relationship between the haplotypes and the susceptibility to ARMD (Table 4).

**Discussion**

Similar to numerous epidemiologic studies [27, 28], we found that the risk of ARMD has strong associations with cigarette smoking and outdoor workplace. When considering the occupationally sunlight exposure and smoking habit (risk factors for ARMD), it becomes apparent that these factors have well-documented effects on oxidative stress and its consequent inflammation. Moreover, oxidative stress has a variety of consequences that can affect disease progression through numerous avenues [29].

**Table 3** Linkage disequilibrium between Ala499Val, PAT, and Lys939Gln polymorphisms of XPC among healthy controls and age-related macular degeneration patients

| Polymorphisms | Ala499Val | PAT | Lys939Gln |
|---------------|-----------|-----|-----------|
| Ala499Val     | –         | \( \chi^2 = 1.0 \) | \( \chi^2 = 1.0 \) |
|               | \( r^2 = 0.2533 \) | \( r^2 = 0.2566 \) | \( r^2 = 0.2875 \) |
|               | \( \chi^2 = 59.77 \) | \( \chi^2 = 62.89 \) | \( \chi^2 = 69.01 \) |
|               | \( P = 1.0 \times 10^{-14} \) | \( P = 2.1 \times 10^{-15} \) | \( P = 9.7 \times 10^{-17} \) |
| PAT           | \( \chi^2 = 1.0 \) | –   | \( \chi^2 = 1.0 \) |
|               | \( r^2 = 0.2875 \) | –   | \( r^2 = 0.2924 \) |
|               | \( \chi^2 = 69.01 \) | –   | \( \chi^2 = 70.17 \) |
|               | \( P = 9.7 \times 10^{-17} \) | –   | \( P = 5.4 \times 10^{-17} \) |
| Lys939Gln     | \( \chi^2 = 1.0 \) | \( \chi^2 = 1.0 \) | –         |
|               | \( r^2 = 0.2924 \) | \( r^2 = 0.2994 \) | –         |
|               | \( \chi^2 = 70.17 \) | \( \chi^2 = 236.03 \) | –         |
|               | \( P = 5.4 \times 10^{-17} \) | \( P = 2.8 \times 10^{-53} \) | –         |

The upper and lower parts of the table showed parameters among healthy controls and age-related macular degeneration patients, respectively.

**Table 4** The association between the haplotypes of the studied XPC polymorphisms and the risk of age-related macular degeneration

| Polymorphisms | Controls | Cases | OR | 95% CI | \( P \) |
|---------------|----------|-------|----|--------|--------|
| 499 PAT       | 939      |       |    |        |        |
| Ala + Gln     | 113      | 118   | 1.0| –      | –      |
| Ala – Lys     | 69       | 66    | 0.91| 0.59–1.40 | 0.686 |
| Val – Lys     | 51       | 55    | 1.03| 0.65–1.63 | 0.891 |
| Ala – Gln     | 3        | 1     | 0.31| 0.03–3.11 | 0.326 |

The frequencies of the 499Val, PAT-, and 939Gln alleles in our control samples were similar to the Caucasian populations [12] and our previous reports from Iran [16, 17]. The XPC Ala499Val, PAT, and Lys939Gln polymorphisms showed linkage disequilibrium in both patient and control groups, as reported in previous reports [12, 17]. We observed only four haplotypes (“Ala + Gln,” “Ala – Lys,” “Val – Lys,” and “Ala - Gln”) out of nine expected haplotypes among our participants, due to linkage disequilibrium in Iranian gene pool. The prevalence of four haplotypes is similar to our previous reports from Iran [17].

Previous studies have indicated that the impaired efficacy of cellular DNA repair may contribute to the pathogenesis of ARMD [5–7]. The XPC is involved in the first step of global genome nucleotide excision DNA repair pathway [8]. Considering that the Ala499Val, Lys939Gln, and PAT polymorphisms are associated with cellular DNA repair capacity [11], we hypothesized that the above-mentioned genetic variations might be involved in pathogenesis of ARMD. However, our present findings indicate that the studied genetic polymorphisms are not significantly associated with the risk of ARMD.

As we know, there are two types of ARMD. The patients included in the present study had exudative AMRD. It has been reported that a genetic polymorphism may be associated with a specific type of a multifactorial trait. For example, several genetic polymorphisms affect the risk of early or late onset bipolar disorder type 1 in different manners [30–32]. It is suggested that there is the same story for association between XPC polymorphisms and dry or exudative AMRD. It should be noted that among the known genetic variations, the polymorphisms of complement factor H (CFH) contribute to more than 50% of disease risk, which is the first major disease-related gene for ARMD [33]. In the present study, we did not determine the CFH genotypes. It should be noted that this may mask the effect of XPC polymorphisms. Further studies are needed to investigate the synergistic effect of common polymorphisms in XPC and CFH on predisposition to ARMD.

Considering the limited sample size in the present case-control study, further larger scaled and well-
designed studies are needed to confirm our results, and before the final conclusion regarding the involvement of the common XPC polymorphisms in age-related macular degeneration can be drawn.

Conclusions
In the present case-control study, the association between three common XPC genetic variations and the risk of ARMD was evaluated. No significant relationship was found between the genotypes of each XPC polymorphisms and the risk of ARMD. There was also no association between the haplotypes of the study polymorphisms and the risk of ARMD.

Abbreviations
ARMD: Age-related macular degeneration; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio; ROS: Reactive oxygen species; CFH: Complement factor H; CI: Confidence intervals; XPC: Xeroderma pigmentosum complementation group

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Authors’ contributions
MS designed the research; SK performed genotyping; SK and MS performed the statistical analyses; SK and MS interpreted the results. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study is approved by the ethics committee of Shiraz University (Iran). A written informed consent form was obtained from each patient according to the Declaration of Helsinki.

Consent for publication
Consent to publish the data was obtained from all individual participants or their attendants included in the study.

Competing interests
The authors declare that they have no conflict of interest.

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