Common polymorphisms of the \textit{hOGG1}, \textit{APE1} and \textit{XRCC1} genes correlate with the susceptibility and clinicopathological features of primary angle-closure glaucoma

Kun Zeng\textsuperscript{1*}, Bo Zhong\textsuperscript{2*}, Min Fang\textsuperscript{1}, Xiao-Li Shen\textsuperscript{1} and Li-Na Huang\textsuperscript{1}

\textsuperscript{1}Shenzhen Key Laboratory of Ophthalmology, Shenzhen Eye Hospital, Shenzhen 518000, P.R. China; \textsuperscript{2}Department of Stomatology, Shenzhen Second People’s Hospital, Shenzhen 518035, P.R. China

Correspondence: Kun Zeng (kunzeng_ab@163.com)

The present case study aims to elucidate the correlation between the human 8-hydroxyguanine-glycosylase (\textit{hOGG1}), \textit{APE1} and X-ray repair cross-complementing gene 1 (\textit{XRCC1}) gene polymorphisms to the susceptibility and clinicopathological features of primary angle closure glaucoma (PACG) in a Chinese Han population. Blood samples were obtained from 258 PACG patients (case group) and 272 healthy volunteers (control group). PCR with sequence-specific primer (PCR-SSP) was used to determine the allele frequencies and genotype distributions of the \textit{hOGG1}, \textit{APE1} and \textit{XRCC1} genes. The risk factors of PACG were determined using logistic regression analysis. The results indicated that \textit{hOGG1} Ser326Cys, \textit{APE1} Asp148Glu and \textit{XRCC1} Arg399Gln polymorphisms were correlated with the risk of PACG. Furthermore, there were thicker corneas, higher intraocular pressure (IOP) and a shorter axial length in patients carrying the mutant genotypes of \textit{XRCC1} Ser326Cys, \textit{APE1} Asp148Glu (Asp/Glu + Glu/Glu) and \textit{XRCC1} Arg399Gln (Arg/Gln + Gln/Glu) than those carrying the corresponding wild-type genotypes. According to the logistic regression analysis, Asp148Glu and Arg399Gln polymorphisms, a short axial length and high IOP are major risk factors for PACG. These findings reveal that \textit{hOGG1} Ser326Cys, \textit{APE1} Asp148Glu and \textit{XRCC1} Arg399Gln polymorphisms are correlated with the risk and clinicopathological features of PACG in a Chinese Han population.

Introduction

Glaucoma is characterized by a progressive degeneration of retinal ganglion cells (RGCs) and optic nerve axons. It also causes damage to the visual field and has been listed as the second highest cause of blindness worldwide [1]. Globally, it is estimated that 60 million people suffer from glaucomatous optic neuropathy and glaucoma is the cause of blindness in 8.4 million people [2]. Nowadays, ethnicity, gender and age are identified as risk factors for primary angle closure glaucoma (PACG) [3]. Although PACG is a leading cause of irreversible blindness, visual ability can be maintained if early and proper treatment is adopted [4]. According to recent reports, gene polymorphism is an important factor in determining an individual’s disease susceptibility, phenotype and treatment response. Furthermore, gene polymorphism is reported to be strongly correlated with glaucoma susceptibility [5,6].

Human 8-hydroxyguanine-glycosylase (\textit{hOGG1}) is a DNA-repair enzyme which can target and remove 8-dihydro-8-oxoguanine (8-OH-G) to repair damaged DNA [7]. The \textit{APE1} gene is located on chromosome 14q11.2-q12 and the amino acid alterations at codon 148 (Asp/Glu) in exon 5 is a common research topic. This polymorphism may be related to ionizing radiations hypersensitivity [8]. \textit{APE1} is capable of
Table 1 Variation of hOGG1, APE1 and XRCC1 SNPs

| Gene   | dbSNP    | Function | Alleles    | Allele frequency (CHB) |
|--------|----------|----------|------------|------------------------|
| hOGG1  | Ser26Cys | Missense | Ser/Cys    | A: 0.7050, B: 0.2950   |
| APE1   | Asp148Glu| Missense | Asp/Glu    | A: 0.5665, B: 0.4335   |
| XRCC1  | Arg399Gln| Missense | Arg/Gln    | A: 0.2317, B: 0.7683   |

CHB, HapMap database for Han Chinese in Beijing.

hydrolysing 3'-blocking fragments from oxidized DNA and is involved in the creation of 3'-hydroxyl nucleotide termini, is a crucial factor of ligation at single- or double-strand breaks and DNA repair synthesis [8]. X-ray repair cross-complementing gene 1 (XRCC1) has been shown to contribute to the repair of damaged DNA [9]. At present, multiple genes and genetic loci that lead to glaucoma have been found, most of which are related to primary open angle glaucoma (POAG) [10]. There are reports that suggest an association among the hOGG1, APE1 and XRCC1 genes and a susceptibility to oesophageal, breast and bladder cancer [11-13]. hOGG1, APE1 and XRCC1 initiates base excision repair (BER) [14-16] and it plays a role in the development of POAG [17]. The present study aims to explore the potential association of hOGG1, XRCC1 and APE1 gene polymorphisms with the susceptibility and clinicopathological features of PACG in a Chinese Han population. We hope to provide a theoretical foundation for the early diagnosis of PACG.

Materials and methods

Study subjects

Han PACG patients (n=258) receiving treatment from February 2008 to October 2014 in the Department of Ophthalmology at Shenzhen Eye Hospital were selected as the case group (141 males and 117 females aged between 37 and 83 years old with an average age of 59.3 ± 6.7 years). Among them, there were 151 acute angle-closure glaucoma (AACG) patients and 107 chronic angle closure glaucoma (CAG) patients. Meanwhile, 272 healthy volunteers were recruited as the control group. There was no significant difference in age, gender or ethnicity between the case and control groups. The inclusion criteria are based on the diagnostic criteria for PACG issued by the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) [18]: (i) primary angle closure suspect (PACS): an eye in which appositional contact between the peripheral iris and posterior trabecular meshwork is considered possible, (ii) primary angle closure (PAC): an eye with an occludable angle and features indicating that trabecular obstruction by the peripheral iris has occurred. The optic disc does not have glaucomatous damage, (iii) PACG: PAC together with evidence of glaucomatous optic neuropathy. The exclusion criteria were: (i) patients with other eye diseases that may lead to a damaged optic nerve or retina, (ii) patients with a family history of genetic disease other than PACG, (iii) patients with secondary glaucoma or open-angle glaucoma, (iv) patients with various chronic diseases, tumours or have a poor liver and kidney functioning. This research was approved by ethics committee of Shenzhen Eye Hospital and informed consent was signed by all the participants.

Single nucleotide polymorphism screening

The single nucleotide polymorphism (SNPs) of hOGG1, APE1 and XRCC1 genes in a Chinese Han population were obtained from the HapMap database. The data were imported into the Haploview Software (version: 4.2) to select tag SNPs based on the following criteria: $r^2 > 0.8$ and minor allele frequency (MAF) > 0.05. The confidence interval method of linkage disequilibrium value (D’ value), the adjacent SNP of D’ value 95% confidence interval (CI) between 0.70 and 0.98 was classified into the same haplotype block. The tag SNP Ser326Cys was selected from the hOGG1 gene, Asp148Glu from the APE1 gene and Arg399Gln from the XRCC1 gene. The SNPs site variation information is shown in Table 1.

SNP sequencing

Five millilitres of elbow vein blood was drawn from all the fasting subjects, anticoagulated with EDTA and preserved in a refrigerator at −70°C. Genomic DNA from the peripheral venous blood was extracted using the phenol–chloroform extraction method. SNP sequencing was performed using the TaqMan probe method. Multiple PCR with the sequence-specific primer (PCR-SSP) method was used to amplify hOGG1, APE1 and XRCC1 genotyping. PCR primers were designed using the Primer Premier Software (version: 5.0) and synthesized at the Beijing Institute of Genomics (Beijing, China). The sequence of each primer is shown in Table 2. The PCR reaction system
Table 2 Primer sequences of hOGG1, APE1 and XRCC1 gene polymorphisms

| Gene   | Primer sequence                  | Product length |
|--------|----------------------------------|----------------|
| hOGG1  | Forward: 5′-TTGATGGGTCACAGAAAGGG-3′ | 552 bp         |
|        | Reverse: 5′-TGAGGTAGTCACAGGGAGGC-3′ | 447 bp         |
| APE1   | Forward: 5′-GAGGAATTGGAGCGTTAAGTGT-3′ | 168 bp         |
|        | Reverse: 5′-GCTTTACACAGAAAGCC-3′  |                |
| XRCC1  | Forward: 5′-TCCTGCGCGCTGAGTTTCT-3′ |                |
|        | Reverse: 5′-TGCCGTGTAGGGCGTTACCTC-3′ |               |

Figure 1. Agarose gel electrophoresis and PCR products of hOGG1 Ser326Cys (Ser/Cys). SNP Ser326 of hOGG1 gene exhibited fragment 446 bp after amplification, which caused three different fragments (194, 252 and 446 bp).

The homozygous wild-type (Ser/Ser) was 252 and 446 bp, the homozygous mutation (Cys/Cys) was 194 and 446 bp and heterozygote (Ser/Cys) was 194, 252 and 446 bp.

Statistical analysis

Statistical software (version: SPSS19.0) was used for all the data analysis. Measurement data are expressed as mean ± S.D. (X ± s) and was examined by the t test. Count data are expressed as a percentage or ratio and was tested with the χ^2 or Fisher’s exact tests. The χ^2 test was used to analyse whether the genotype distributions of hOGG1, APE1, XRCC1 and the control group were in accordance with the Hardy–Weinberg equilibrium. Logistic regression analysis was applied to analyse the influence factors of PACG. The P-value was two-sided and a P<0.05 indicated statistical significance.

Results

Genotyping of hOGG1, APE1 and XRCC1 polymorphisms

SNPs of hOGG1, APE1 and XRCC1 were analysed using multiple PCR. Identifying the specific alleles on each primer allowed for PCR amplified fragments (which were digested by enzymes of the four polymorphic sites) to be obtained. The genotypes gained by DNA sequencing were the same as those gained through the PCR-SSP method (Figures 1-3).
Figure 2. Agarose gel electrophoresis and PCR products of APE1 Asp148Glu (Asp/Glu). SNP 148 of APE1 gene exhibited fragment 403 bp after amplification, which caused three different fragments (167, 236 and 403 bp). The homozygous wild-type (Asp/Asp) was 236 and 403 bp, the homozygous mutation (Glu/Glu) was 194 and 446 bp and heterozygote (Asp/Glu) was 167, 236 and 403 bp.

Figure 3. Agarose gel electrophoresis and PCR products of XRCC1 Arg399Gln (Arg/Gln). SNP 399 of XRCC1 gene exhibited fragment 447 bp after amplification, which caused three different fragments (447, 222 and 669 bp). The homozygous wild-type (Arg/Arg) was 447 and 669 bp, the homozygous mutation (Gln/Gln) was 463 and 669 bp and heterozygote (Arg/Gln) was 222, 447 and 669 bp.

Hardy–Weinberg equilibrium testing of the genotype distributions of hOGG1, APE1 and XRCC1 gene polymorphisms in the control group

The genotype frequency of the control group was in accordance with the Hardy–Weinberg equilibrium. After the Hardy–Weinberg equilibrium testing, the genotype frequencies of the hOGG1, APE1 and XRCC1 genes in the control group showed no significant difference from each other (all \( P > 0.05 \)). This indicates that the sample was a good representation of the population.

Comparison of clinicopathological characteristics between the case and control groups

As shown in Table 3, there was no significant difference in gender, age and diastolic pressure between the case and control groups (all \( P > 0.05 \)). However, patients in the case group exhibited a remarkably lower eyesight ability, shorter axial length, higher systolic pressure and intraocular pressure (IOP) and thicker cornea than the control group (all \( P < 0.05 \)).
Allele frequencies and genotype distributions of \textit{hOGG1} Ser326Cys, \textit{APE1} Asp148Glu and \textit{XRCC1} Arg399Gln in the case and control groups

Allele and genotype frequency distributions of \textit{hOGG1} Ser326Cys, \textit{APE1} Asp148Glu and \textit{XRCC1} Arg399Gln in the case and control groups are shown in Table 4. The genotype distributions of the case and control groups were tested through linkage disequilibrium. The results show that \textit{hOGG1} Ser326Cys and \textit{APE1} Asp148Glu had D' and r² values of 0.991 and 0.824 respectively; \textit{hOGG1} Ser326Cys and \textit{XRCC1} Arg399Gln had D' and r² values of 0.993 and 0.871 respectively; \textit{APE1} Asp148Glu and \textit{XRCC1} Arg399Gln had D' and r² values of 0.995 and 0.875 respectively (Figure 4). The risk of PACG is associated with \textit{hOGG1} Ser326Cys (Ser/Ser compared with Cys/Cys: odds ratio (OR) = 1.788, \textit{P}=0.018; Ser/Ser compared with (Ser/Cys + Cys/Cys): OR = 1.821, \textit{P}=0.002; Serine compared with Cysteine: OR = 1.367, \textit{P}=0.011). \textit{APE1} Asp148Glu is associated with PACG risk (Asp/Asp compared with Glu/Glu: OR = 1.833, \textit{P}=0.021; Asparagine compared with Glutamic acid: OR = 1.323, \textit{P}=0.023). \textit{XRCC1} Arg399Gln is also associated with PACG risk (Arg/Arg compared with Glu/Glu: OR = 2.491, \textit{P}=0.008; Arg/Arg compared with (Arg/Gln + Glu/Glu): OR = 1.796, \textit{P}=0.001; Arginine compared with Glutamic acid: OR = 1.574, \textit{P}=0.001).
Correlation of hOGG1 Ser326Cys, APE1 Asp148Glu and XRCC1 Arg399Gln polymorphisms with the clinicopathological features of PACG patients

There was no difference in gender, age, diseased eye, eyesight and blood pressure among the different polymorphisms of hOGG1, APE1 and XRCC1 (all P > 0.05). However, patients carrying the mutation genotype of hOGG1 Ser326Cys (Ser/Cys + Cys/Cys) had thicker corneas, higher IOP and shorter axial lengths than those with the Ser/Ser wild-type genotype of hOGG1 Ser326Cys. Patients with the mutation genotype of APE1 Asp148Glu (Asp/Glu + Glu/Glu) showed thicker corneas, higher IOP and shorter axial lengths than those with the Asp/Asp wild-type genotype. Furthermore, there were thicker corneas, higher IOP and shorter axial lengths in carriers with the mutation genotype of XRCC1 Arg399Gln (Arg/Gln + Glu/Glu) than those with the Arg/Arg wild-type genotype (all P < 0.05) (Table 5).

Logistic regression analysis on the risk factors of PACG

A binary logistic regression analysis was conducted using PACG as the dependent variable and the Ser/Ser genotype of the Ser326Cys site, the Asp/Asp genotype of the Asp148Glu site, the Arg/Arg genotype of the Arg399Gln site, cornea thickness, IOP and axial length as the independent variables. As shown in Table 6, Asp148Glu and Arg399Gln polymorphisms could increase PACG risk (both P < 0.05). It was also shown that Ser326Cys polymorphisms and cornea thickness had little influence on the occurrence of PACG, whereas a high IOP and short axial length are major risk factors of PACG (all P < 0.05).

Discussion

PACG is a major type of glaucoma in many Southeast Asian countries [19] and many PACG patients have similar anatomic features such as a shallow anterior chamber, increased lens thickness, anterior position of the lens, narrow anterior chamber angles and a short axial length [20]. Genetic factors have been documented to be associated with the development of PACG [21]. Genes involved in PACG susceptibility have been widely explored and the association between individual gene polymorphisms and PACG susceptibility has been noticed [20,22,23]. However, there are no reports on the association of hOGG1, APE1 and XRCC1 gene polymorphisms with PACG susceptibility and characteristic features, therefore, the current study was conducted.

The DNA repair enzyme system is important in maintaining the stability of a cell group and protects the cell genome from carcinogenesis by repairing damaged DNA. XRCC, XP and hOGG1 are common repair enzymes [24]. It has been found that the genetic diversity of repair enzymes affects both disease susceptibility and a tumour's biological behaviour [25]. hOGG1 is an important enzyme which removes 8-OH-G in DNA and has been found to possess SNP characteristics. Its gene mutation affects the enzymatic activity of hOGG1 and may lead to defects in DNA repair [26]. hOGG1 Ser326Cys polymorphism reduces the DNA repair ability of hOGG1 proteins [27]. This may explain the association between hOGG1 polymorphism and the elevated risk of PACG. Evidence shows that the hOGG1 gene is especially important for in vitro DNA single-strand break repair and that the in vitro DNA-repair ability
of the Cys/Cys homozygous genotype and Ser/Cys hybrid is significantly lower than that of the Ser/Ser wild-type genotype [28,29]. It has also been found that the cells with hOGG1-Ser326 protein expression are more effective in inhibiting mutations induced by 8-OH-G than hOGG1-Cys326. This indicates a relatively low repair ability of hOGG1-Cys326 in human cells [30]. Therefore, hOGG1 Ser326Cys polymorphism lowers the DNA repair ability of the hOGG1 protein and increases the risk of PACG.

Base excision repair (BER) is the main DNA repair pathway that repairs damaged DNA bases caused by oxidative and alkylating reagents and plays an important role in the maintenance of DNA integrity [31,32]. APE1 is the key rate-limiting enzyme in the BER process and as a redox factor, can regulate the DNA-binding activity of transcription factors [33,34]. This is one mechanism that relates APE1 Asp148Glu polymorphism to PACG susceptibility. APE1 Asp148Glu is also a common APE1 polymorphism site. Mutation of the site nucleotide Glutamic acid into Aspartic acid leads to increased chromosomal damage, reduces DNA repair ability and increases PACG susceptibility.

XRCC1 plays a critical role in BER [35]. Its polymorphic site (XRCC1 Arg399Gln) is located in the binding domain of PARP (BRCT-1) and has a great affect on protein function. The mutation of Glutamine on the Arg399Gln site into Arginine leads to the mutation of amino acid Arginine in the 399th codon encoding into Glutamine. This reduces the DNA repair ability of XRCC1 [36] and increases the risk of PACG. Previous studies have found that XRCC1 gene diversity is related with the prevalence of nasopharyngeal carcinoma, laryngeal cancer and liver cancer [37-39]. It has

Table 5 Correlation of gene polymorphisms of hOGG1, APE1 and XRCC1 with clinicopathological features of PACG patients

| Clinicopathological features | hOGG1 Ser326Cys | APE1 Asp148Glu | XRCC1 Arg399Gln |
|-----------------------------|----------------|---------------|----------------|
|                             | Ser/Ser        | Ser/Cys + Cys/Cys | Asp/Asp | Asp/Glu + Glu/Glu | Arg/Arg | Arg/Gln + Glu/Glu |
| Gender                      |                |                |            |                |         |                 |
| Male                        | 34             | 107            | 26         | 115            | 57      | 84              |
| Female                      | 24             | 93             | 18         | 99             | 46      | 71              |
| Age (years)                 |                |                |            |                |         |                 |
| ≤60                         | 28             | 113            | 25         | 116            | 58      | 83              |
| >60                         | 30             | 87             | 19         | 98             | 45      | 72              |
| Disease eye                 |                |                |            |                |         |                 |
| Both eyes                   | 26             | 90             | 16         | 100            | 46      | 70              |
| One eye                     | 32             | 110            | 28         | 114            | 57      | 85              |
| Eyesight                    |                |                |            |                |         |                 |
| ≤0.5                        | 33             | 139            | 29         | 143            | 63      | 109             |
| >0.5                        | 25             | 61             | 15         | 71             | 40      | 46              |
| Blood pressure              |                |                |            |                |         |                 |
| Systole (mmHg)              | 141.9±9.4      | 140.2±8.2      | 143.0±10.1 | 140.1±8.2      | 141.5±9.3 | 140.0±8.2 |
| Diastole (mmHg)             | 86.6±6.7       | 86.0±6.5       | 88.2±8.0   | 85.9±6.4       | 86.6±7.0  | 85.8±6.2       |
| Eye condition               |                |                |            |                |         |                 |
| Axial length (mm)           | 25.4±8.2       | 21.9±7.5*      | 26.1±9.4   | 22.0±7.5†      | 24.06±7.4 | 21.3±7.5†      |
| Corneal thickness (μm)      | 527.9±7.3      | 547.6±10.2*    | 523.3±5.8  | 546.8±10.1†    | 532.1±6.8 | 550.7±9.4†    |
| IOP (mmHg)                  | 20.2±5.3       | 25.4±7.1*      | 20.1±6.0   | 25.0±7.0†      | 20.7±5.2  | 26.6±7.1†      |

*, P<0.05 in comparison with Ser/Ser wild-type genotype; †, P<0.05 in comparison with Asp/Asp wild-type genotype; ‡, P<0.05 in comparison with Arg/Arg wild-type genotype.

Table 6 Logistic regression analysis for the risk factors of PACG

| Independent variable | B      | S.E.M. | P     | OR   | 95% CI          |
|---------------------|--------|--------|-------|------|-----------------|
| Ser326Cys           | −0.383 | 0.275  | 0.164 | 0.682 | 0.397–1.169     |
| Asp148Glu           | −1.059 | 0.341  | 0.002 | 2.251 | 1.958–3.261     |
| Arg399Gln           | −0.859 | 0.295  | 0.004 | 1.635 | 1.226–2.183     |
| Axial length        | −0.844 | 0.093  | 0     | 1.782 | 1.563–2.377     |
| Cornea thickness    | 0.019  | 0.016  | 0.231 | 1.019 | 0.988–1.051     |
| IOP                 | 1.138  | 0.225  | <0.001| 3.121 | 2.007–4.854     |
also been demonstrated that XRCC1 Arg399Gln is correlated with the incidence of the above-mentioned tumours and that allele Gln increases the risk of these tumours. Similarly, the present study also found that XRCC1 Arg399Gln polymorphism is associated with the risk of PACG.

In summary, hOGG1, APE1 and XRCC1 gene polymorphisms are associated with the risk and characteristic features of PACG and therefore, can be used as biological indicators for PACG. However, there are limitations to our study. Glaucoma is a disease that involves many factors and multiple genes. The effect of various factors can easily be offset by another and lead to misleading results. Moreover, there are distribution differences among hOGG1, APE1 and XRCC1 gene polymorphisms in different regions. As the sample size is limited, it is necessary to carry out case-controlled researches in different ethnic groups, have larger sample sizes and use multi-factor analysis to further confirm our results.

Acknowledgements
We thank the helpful comments received on the present paper from our reviewers.

Author contribution
K.Z., X.-L.S., M.F. and L.N.H. participated in the design, funding applications, interpretation of the results and drafting of the article. L.N.H. and D.H.M. contributed to data collection. All authors read and approved the final manuscript.

Competing interests
The authors declare that there are no competing interests associated with the manuscript.

Funding
The authors declare that there are no sources of funding to be acknowledged.

Abbreviations
APE1, apurinic endonuclease 1; BER, base excision repair; CI, confidence interval; dbSNP, Database of Single Nucleotide Polymorphisms; D' value, disequilibrium value; hOGG1, human 8-hydroxyguanine glycosylase; IOP, intraocular pressure; OR, odds ratio; PAC, primary angle closure; PACG, primary angle closure glaucoma; PCR-SSP, PCR with sequence-specific primer; POAG, primary open angle glaucoma; SNP, single nucleotide polymorphism; XRCC1, X-ray repair cross-complementing gene 1.

References
1 Yasumura, R., Meguro, A., Ota, M., Nomura, E., Uemoto, R., Kashiwagi, K. et al. (2011) Investigation of the association between SLC1A3 gene polymorphisms and normal tension glaucoma. Mol. Vis. 17, 792–796
2 Cook, C. and Foster, P. (2012) Epidemiology of glaucoma: what’s new? Can. J. Ophthalmol. 47, 223–226
3 van Romunde, S.H., Thepass, G. and Lemij, H.G. (2013) Is hyperopia an important risk factor for pacg in the dutch population? A case control study. J. Ophthalmol. 2013, 630481
4 Chen, M.S., Chang, C.C., Lin, C.P., Wang, P.C., Lin, L.R., Hou, P.K. et al. (2012) Role of vascular endothelial growth factor in the breakdown of the blood-aqueous barrier after retinal laser photocoagulation in pigmented rabbits. J. Ocul. Pharmacol. Ther. 28, 83–88
5 Costa, N.B., Silva, C.T., Frare, A.B., Silva, R.E. and Moura, K.K. (2014) Association between CYP1A1m1 gene polymorphism and primary open-angle glaucoma. Genet. Mol. Res. 13, 10382–10389
6 Lee, Y.H. and Song, G.G. (2015) TNF-α -308 A/G and -238 A/G polymorphisms and susceptibility to glaucoma: a meta-analysis. Genet. Mol. Res. 14, 4966–4977
7 Karitlata, P., Kauppila, S., Puistola, U. and Jukkola-Vuorinen, A. (2012) Absence of the DNA repair enzyme human 8-oxoguanine glycosylase is associated with an aggressive breast cancer phenotype. Br. J. Cancer. 106, 344–347
8 Gu, D., Wang, M., Wang, S., Zhang, Z. and Chen, J. (2011) The DNA repair gene APE1 T1349G polymorphism and risk of gastric cancer in a Chinese population. PLoS ONE 6, e28971
9 Bu, T., Liu, L., Sun, Y., Zhao, L., Peng, Y., Zhou, S. et al. (2014) XRCC1 Arg399Gln polymorphism confers risk of breast cancer in American population: a meta-analysis of 10846 cases and 11723 controls. PLoS ONE 9, e86086
10 Takamoto, M. and Araie, M. (2014) Genetics of primary open angle glaucoma. Jpn. J. Ophthalmol. 58, 1–15
11 He, J., Gii, L.X., Wang, M.Y., Hua, R.X., Zhang, R.X., Yu, H.P. et al. (2012) Polymorphisms in the XPG gene and risk of gastric cancer in Chinese populations. Hum. Genet. 131, 1235–1244
12 Shen, E., Liu, C., Wei, L., Hu, J., Weng, J., Yin, Q. et al. (2014) The APE1 Asp148Glu polymorphism and colorectal cancer susceptibility: a meta-analysis. Tumour Biol. 35, 2529–2535
13 Mao, Y., Xu, X., Lin, Y., Chen, H., Wu, J., Hu, Z. et al. (2013) Quantitative assessment of the associations between XRCC1 polymorphisms and bladder cancer risk. World J. Surg. Oncol. 11, 58
14 Vidal, A.E., Hickson, I.D., Boiteux, S. and Radicella, J.P. (2001) Mechanism of stimulation of the DNA glycosylase activity of hOGG1 by the major human AP endonuclease: bypass of the AP lyase activity step. *Nucleic Acids Res.* **29**, 1285–1292

15 Fishel, M.L. and Kelley, M.R. (2007) The DNA base excision repair protein Apel/Ref-1 as a therapeutic and chemopreventive target. *Mol. Aspects Med.* **28**, 375–395

16 Zhang, X., Miao, X., Liang, G., Hao, B., Wang, Y., Tan, W. et al. (2005) Polymorphisms in DNA base excision repair genes ADPRT and XRCC1 and risk of lung cancer. *Cancer Res.* **65**, 722–726

17 Cuchra, M., Markiewicz, L., Mucha, B., Pytel, D., Szymanek, K., Szemraj, J. et al. (2015) The role of base excision repair in the development of primary open angle glaucoma in the Polish population. *Mutat. Res.* **778**, 26–40

18 Sun, X., Dai, Y., Chen, Y., Yu, D.Y., Cringle, S.J., Chen, J. et al. (2017) Primary angle closure glaucoma: what we know and what we don’t know. *Prog. Retin. Eye Res.* **57**, 26–45

19 Oued, D.T.L., Nongpiur, M.E., Perera, S.A. and Aung, T. (2011) Angle imaging: advances and challenges. *Indian J. Ophthalmol.* **59**, S69–S75

20 Awadalla, M.S., Burdon, K.P., Kuot, A., Hewitt, A.W. and Craig, J.E. (2011) Matrix metalloproteinase-9 genetic variation and primary angle closure glaucoma in a Caucasian population. *Mol. Vis.* **17**, 1420–1424

21 Ahram, D.F., Alward, W.L. and Kuehn, M.H. (2015) The genetic mechanisms of primary angle closure glaucoma. *Eye* **29**, 1251–1259

22 Nongpiur, M.E., Wei, X., Xu, L., Perera, S.A., Wu, R.Y., Zheng, Y. et al. (2013) Lack of association between primary angle-closure glaucoma susceptibility loci and the ocular biometric parameters anterior chamber depth and axial length. *Invest. Ophthalmol. Vis. Sci.* **54**, 5824–5828

23 Wei, X., Nongpiur, M.E., de Leon, M.S., Baskaran, M., Perera, S.A., How, A.C. et al. (2014) Genotype-phenotype correlation analysis for three primary angle closure glaucoma-associated genetic polymorphisms. *Invest. Ophthalmol. Vis. Sci.* **55**, 1143–1148

24 Druzhinin, V.G., Volkov, A.N., Glushkov, A.N., Golovina, T.A., Minina, V.I., Ingel’, F.I. et al. (2011) Role of repair gene polymorphism in estimating the sensitivity of human genome to radon in concentrations exceeding maximum permissible level. *Gig. Saniit.* **26**, 30

25 Al-Harithy, R.N. and Al-Zahrani, M.H. (2012) The adipopectin gene, ADIPQ, and genetic susceptibility to colon cancer. *Oncol. Lett.* **3**, 176–180

26 Goksuzu, C., Cakmakoglu, B., Dasdemir, S., Tulbas, F., Elitok, A., Tamer, S. et al. (2013) Association between genetic variants of DNA repair genes and coronary artery disease. *Genet. Test Mol. Biomarkers.* **17**, 307–313

27 Li, Q., Huang, L., Rong, L., Xue, Y., Lu, Q., Rui, Y. et al. (2011) hOGG1 Ser326Cys polymorphism and risk of childhood acute lymphoblastic leukemia in a Chinese population. *Cancer Sci.* **102**, 1123–1127

28 Khlifi, R., Rebal, A. and Hamza-Chaffai, A. (2012) Polymorphisms in human DNA repair genes and head and neck squamous cell carcinoma. *J. Genet.* **91**, 375–384

29 Aka, P., Matteua, R., Buchet, J.P., Thieren, H. and Kirsch-Volders, M. (2004) Are genetic polymorphisms in OGG1, XRCC1 and XRCC3 genes predictive for the DNA strand break repair phenotype and genotoxicity in workers exposed to low dose ionising radiations? *Mutat. Res.* **556**, 169–181

30 Yamane, A., Kohno, T., Ito, K., Sunaga, N., Aoki, K., Yoshimura, K. et al. (2004) Differential ability of polymorphic OGG1 proteins to suppress mutagenesis induced by 8-hydroxyguanine in human cell in vivo. *Carcinogenesis* **25**, 1689–1694

31 Krokan, H.E. and Bjoras, M. (2013) Base excision repair. *Cold Spring Harb. Perspect. Biol.* **5**, a012583

32 Kong, X., Stephens, J., Ball, Jr, A.R., Heale, J.T., Newkirk, D.A., Berns, M.W. et al. (2011) Condensin I recruitment to base damage-enriched DNA lesions is modulated by PARP1. *PLoS ONE* **6**, e23548

33 Wu, B., Liu, H.L., Zhang, S., Dong, X.R. and Wu, G. (2012) Lack of an association between two BER gene polymorphisms and breast cancer risk: a meta-analysis. *PLoS ONE* **7**, e50857

34 Cun, Y., Dai, N., Li, M., Xiong, C., Zhang, Q., Su, J. et al. (2014) APE1/Ref-1 enhances DNA binding activity of mutant p53 in a redox-dependent manner. *Oncol. Rep.* **31**, 901–909

35 Horton, J.K., Stefanick, D.F., Gassman, N.R., Williams, J.G., Gabel, S.A., Cuneo, M.J. et al. (2013) Preventing oxidation of cellular XRCC1 affects PARP-mediated DNA damage responses. *DNA Repair (Amst.)* **12**, 774–785

36 Yang, H.Y., Yang, S.Y., Shao, F.Y., Wang, H.Y. and Wang, Y.D. (2015) Updated assessment of the association of the XRCC1 Arg399Gln polymorphism with lung cancer risk in the Chinese population. *Asian Pac. J. Cancer Prev.* **16**, 495–500

37 Chen, W., Wang, Z.Y., Xu, F.L., Wu, K.M., Zhang, Y., Xu, L. et al. (2014) Association of XRCC1 genetic polymorphism (Arg399Gln) with laryngeal cancer: a meta-analysis based on 4,031 subjects. *Tumour Biol.* **35**, 1637–1640

38 Jin, H., Xie, X., Wang, H., Hu, J., Liu, F., Liu, Z. et al. (2014) ERCC1 Cys8092Ala and XRCC1 Arg194Trp polymorphisms predict progression-free survival after curative radiotherapy for nasopharyngeal carcinoma. *PLoS ONE* **9**, e101256

39 Bose, S., Tripathi, D.M., Sukriti, Sakhuja, P., Kazim, S.N. and Sarin, S.K. (2013) Genetic polymorphisms of CYP2E1 and DNA repair genes HOGG1 and XRCC1: association with hepatitis B related advanced liver disease and cancer. *Gene* **519**, 231–237
