Association between the genetic variants of base excision repair pathway genes and allergic rhinitis susceptibility in Chinese children

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ABSTRACT

Background: Allergic rhinitis (AR) is a frequent inflammatory disorder of the upper respiratory tract, which has complex patterns of inheritance. Accumulating evidence has shown the key roles of DNA damage in inflammatory diseases, and the base excision repair (BER) is the primary pathway responsible for DNA repair during inflammation.

Methods: Here, we performed a case-control study to investigate the associations between 20 potentially functional single nucleotide polymorphisms (SNPs) in 6 BER pathway genes (PARP1, hOGG1, FEN1, APEX1, LIG3, and XRCC1) and AR susceptibility in 508 AR cases and 526 controls which originated in China. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for evaluating the association strength.

Results: We found that hOGG1 rs1052133 G>C and XRCC1 rs2682585 G>A polymorphisms were associated with decreased AR risk (adjusted OR = 0.67, 95% CI = 0.47-0.94, P = 0.022; and adjusted OR = 0.21, 95% CI = 0.06-0.79, P = 0.022, respectively). Stratification analysis suggested that: hOGG1 rs1052133 GC/CC genotype reduced AR risk in subjects among following subgroups: age ≤60 months, females, and moderate AR; XRCC1 rs2682585 GG genotype decreased AR risk in subjects age >60 months, and LIG3 rs1052536 TT genotype increased AR risk in subjects of severe AR.

Conclusion: Our findings indicated that the genetic variants of hOGG1, XRCC1, and LIG3 genes might affect AR susceptibility in the Chinese population, which will provide novel insight into the genetic underpinnings of AR from the DNA damage level.

Keywords: Allergic rhinitis, Genetic variants, Susceptibility, Base excision repair
INTRODUCTION

Allergic rhinitis (AR) is a highly prevalent immunoglobulin (Ig)E-mediated upper airway inflammatory disease. The incidence rate of AR is 25–35% worldwide, and its prevalence was rapidly increased in recent decades along with industrialization. Therefore, it is an emergency to identify the genetic markers for risk assessment, early diagnosis, and disease prognosis of AR.

Previous studies have demonstrated that AR is the result of complex interactions between environmental and genetic factors. Environmental factors such as home dampness, fungal allergens, and mold stains are important factors that are strongly associated with AR. However, not all individuals exposed to similar environmental factors develop AR, suggesting that environmental factors may play an important rather than a conclusive role. Growing studies showed that the sequence polymorphisms in various genes and regions are associated with AR susceptibility. The interleukin such as IL-18, IL-4, IL-5, and IL-13 are the crucial regulators that involve in the pathogenesis of AR, numerous genetic studies indicated that single nucleotide polymorphisms (SNPs) in these genes are related to AR susceptibility.

Accumulating studies show that genomic instability could trigger inflammatory responses. DNA damage can activate important inflammatory regulators, such as NFkB, a key transcription factor that induces and accelerates inflammation by promoting the transcription of pro-inflammatory genes. Base excision repair (BER) is the primary pathway responsible for DNA damage repair during inflammation. The BER activity was shown to be crucial for protecting against genetic mutations in animal models of inflammation. The process of BER can be roughly divided into four steps: recognize and excise the damaged base, incise the DNA backbone, fill the nucleotide gap, and seal the remaining gap. A great number of studies indicated that aberrant BER pathway proteins are associated with multiple diseases, such as various cancers.

Functional researches showed that SNPs in the BER pathway genes may modify the expression and the kinetics of BER proteins, which may affect the DNA repair activity of the BER system. However, evidence for the effects of SNPs in the BER pathway genes in the risk of AR remains poor. Therefore, we performed this case-control research to identified more AR susceptibility SNPs from BER pathway genes, which may provide original insights into the diagnosis, grading, and prognosis of AR from the perspective of DNA damage repair.

MATERIALS AND METHODS

Study subjects

In the present case-control study, a total of 508 clinically diagnosed as AR cases and 526 disease-free healthy controls were recruited by doctors of Department of Otolaryngology, XXX from July 2019 to July 2020. The atopic status to common inhalant allergens included dust mites, pollens, pets, molds and cockroach, etc. were examined by skin prick test or the detection of specific IgE levels. The AR was diagnosed by ENT doctors according to typical nasal symptoms, sensitization to allergens confirmed by skin prick test and specific IgE measurement. Patients with other comorbid diseases (such as asthma etc.) were excluded. The demographic characteristics of all subjects are shown in Table 1. AR was graded as follows: mild, when symptoms do not impair sleep, daily activities, and work and/or school performance; moderate, when symptoms impair sleep, daily activities, and work and/or school performance; severe, when symptoms impair sleep, daily activities, and work and/or school performance severely. All participants have signed the informed consent by their guardians and the study protocol was approved by the hospital institutional review board before the study.

Polymorphism selection and genotyping

We screened the functional polymorphisms among the BER pathway genes using the dbSNP database and SNPInfo software. Briefly, we searched the potential candidate SNPs that located in the 5'-flanking region, 5' untranslated region, 3' untranslated region, and exon of 6 selected BER pathway genes. A total of 20 potentially functional SNPs in 6 genes were identified ultimately for assessing the associations with AR risk. Regarding genotyping, the genomic DNA
extraction from the peripheral blood of all subjects was performed through the TIANamp Blood DNA Kit (TianGen Biotech, Beijing, China). The genotyping for selected SNPs of all DNA samples was conducted by the standard TaqMan real-time PCR in the 384-well format. To make sure the credibility of the results, we chose 10% of the DNA samples randomly for a second-time genotyping (a 100% concordance rate was obtained).

**Statistical analysis**

The goodness-of-fit $\chi^2$ test was used to verify whether the included SNPs were in Hardy-Weinberg equilibrium (HWE) among the control subjects. The distributional differences of demographic characteristics and allele frequencies between AR cases and controls were evaluated by the two-sided chi-square test. The associations between selected SNPs and AR risk were assessed by calculating the odds ratios (ORs) and 95% confidence intervals (CIs) in an unconditional logistic regression model. And the adjusted ORs and corresponding 95% CIs that adjusted for age and sex were calculated through unconditional multivariate logistic regression analysis. Furthermore, stratification analysis was conducted according to age, gender, and clinical grading.

The version 9.4 SAS software (SAS Institute, NC, USA) was used for conducting all statistical analyses in this study. It would be considered a statistically significant result when $P$-value $< 0.05$.

**Expression quantitative trait loci (eQTL) analysis**

The expression quantitative trait loci (eQTL) are specific loci locate on genomes, which were

| Variables          | Cases ($n = 508$) | Controls ($n = 526$) | $P$ |
|--------------------|------------------|----------------------|-----|
|                    | No.              | %                    | No.  | %            |
| Age range, month   | 36.00-180.00     | 0.07-156.00          | <0.0001 |
| Mean ± SD ≤60      | 80.74 ± 24.78    | 35.51 ± 28.75        | 422  | 80.23        |
| >60                | 344              | 67.72                | 104  | 19.77        |
| Sex female         | 257              | 50.59                | 241  | 45.82        |
| Sex male           | 251              | 49.41                | 285  | 54.18        |
| Sensitization D1   | 472              | 93                   | -    |
| D2                 | 482              | 95                   | -    |
| Cockroach          | 56               | 11                   | -    |
| Cat                | 42               | 8                    | -    |
| Dog                | 37               | 7                    | -    |
| Others             | 22               | 4                    | -    |
| Total IgE (kAU/L)* | 86.5 (45.5-848.9)|                     |
| Specific IgE (kAU/L)* |                |                     |
| D1                 | 22.3 (5.8-67.3)  |                     |
| D2                 | 15.6 (7.9-48.1)  |                     |
| Cockroach          | 8.1 (2.7-33.6)   |                     |
| Cat                | 3.2 (2.9-25.1)   |                     |
| Dog                | 9.1 (4.3-38.8)   |                     |
| Clinical grading   |                  |                      |
| Mild               | 147              | 28.94                | /    |
| Moderate           | 227              | 44.69                | /    |
| Severe             | 134              | 26.38                | /    |

Table 1. Frequency distribution of selected variables for allergic rhinitis cases and controls. SD, standard deviation; NA, not available.*Geometric mean after logarithmic transformation (95% CI). **Two-sided $\chi^2$ test for distributions between allergic rhinitis cases and controls. **
reported associated with various genes expression. The GTEx project (http://www.gtexportal.org/home/) was designed to assess the associations between genetic polymorphisms and genes mRNA expression in normal human cells or tissues. By the GTEx portal, we performed the eQTL analysis to explore the biological effects of the associated SNPs on neighboring gene expression in cell-cultured fibroblasts. The detail of the analysis has been described in previous studies.17

**RESULTS**

**Associations between SNPs of BER pathway genes and AR risk**

In this case-control study, 508 AR cases and 526 healthy controls were successfully genotyped (Table 1). As display in Table 2, the genotypic distributions of all these selected SNPs are following HWE among the controls (P ≥ 0.05), except for APEX1 rs1130409 (P = 0.003). In the single locus analysis, our results show that two SNPs: hOGG1 rs1052133 G > C (AOR = 0.67, 95% CI = 0.47-0.94, P = 0.022) and XRCC1 rs2682585 G > A (AOR = 0.21, 95% CI = 0.06-0.79, P = 0.022) significantly reduces the risk of AR under dominant model and recessive model, respectively. No significant association was found between the rest SNPs and AR risk under dominant or recessive models (P ≥ 0.05).

**Stratification analysis**

To explore whether the significant SNPs affect the risk of AR among different subgroups, we further carry out the stratified analysis according to age, gender, and severity grading. As shown in Table 3, the hOGG1 rs1052133 GC/CC genotype significantly decreases AR risk in the following subgroups: age ≤60 months (AOR = 0.57, 95% CI = 0.39-0.83, P = 0.004), females (AOR = 0.50, 95% CI = 0.30-0.83, P = 0.008), and moderate AR (AOR = 0.49, 95% CI = 0.32-0.73, P = 0.001) compare with GG genotype. Comparing with the TT/TG genotype, the XRCC1 rs2682585 GG genotype also reduce the risk of AR in the subgroup: age >60 months (AOR = 0.21, 95% CI = 0.05-0.96, P = 0.045). Regarding LIG3 rs1052536, TT genotype significantly increased the AR risk in severe AR patients when compared with CC/CT genotype (AOR = 2.44, 95% CI = 1.13-5.28, P = 0.023). And no significant relevance was detected between LIG3 rs4796030 A > C polymorphism and AR susceptibility among different subgroups (P ≥ 0.05).

**eQTL analysis**

To further investigate the potential biological effects on genes expression of 2 significant SNPs, the eQTL analysis was conducted from the genotype-tissue expression (GTEx) portal. We found that the hOGG1 rs1052133 G allele was relevant to higher mRNA levels of hOGG1, TTLL3, CRELD1 genes compared with the rs1052133C allele in the cultured fibroblasts (Fig. 1A). We also observed that the PINLYP mRNA with XRCC1 rs2682585 G allele was significantly lower than those with XRCC1 rs2682585 A allele in the cell-cultured fibroblasts. In contrast, the XRCC1 rs2682585 G allele significantly up-regulated the mRNA level of the ETHE1 gene compared with the rs2682585 A allele (Fig. 1B).

**DISCUSSION**

The current understanding of the genetic predisposition of AR is still incomplete. Here, we evaluate the association between 20 functional SNPs in 6 core genes of the BER pathway and AR susceptibility. Our study identified two AR risk-associated potential SNPs: hOGG1 rs1052133 and XRCC1 rs2682585, which both are associated with decreased risk of AR. Our findings may contribute to identify the susceptible population and make early interventions to prevent the occurrence of AR.

Numerous studies showed that SNPs in certain crucial genes involved in the pathology of AR are significantly associated with increased or decreased AR susceptibility, such as chemokine, interleukin, and their receptor coding genes.18,19 For example, rs2243250C > T, one SNP located in the promoter region of the IL4 gene, is associated with up-regulated IL-4 gene expression and increases the risk of AR eventually.20,21 The rs1800795 and rs1800796 are located at the IL-6 promoter region, which increases AR risk by up-regulating serum IL-6 levels.22,23

Although DNA damage is generally considered a key event in cancer, growing evidence
| Gene    | SNP    | Allele | Case (N = 508) | Control (N = 526) | Adjusted OR<sup>a</sup> (95% CI) | P<sup>a</sup> | Adjusted OR<sup>b</sup> (95% CI) | P<sup>b</sup> | HWE  |
|---------|--------|--------|----------------|------------------|----------------------------------|-----------|----------------------------------|-----------|------|
| PARP1   | rs1136410 | A G    | 165 239 104 169 261 96 | 0.95 (0.67-1.34) 0.772 | 1.39 (0.92-2.12) 0.120 | 0.785 |
| PARP1   | rs2666428 | T C    | 324 165 19 341 170 15 | 0.97 (0.69-1.36) 0.858 | 0.91 (0.36-2.30) 0.836 | 0.256 |
| PARP1   | rs8679  | A G    | 422 64 2 460 66 0 | 0.96 (0.59-1.57) 0.881 | / | / | 0.125 |
| hOGG1   | rs1052133 | G C    | 190 244 74 156 278 92 | **0.67 (0.47-0.94)** **0.022** | 0.75 (0.48-1.18) 0.215 | 0.094 |
| hOGG1   | rs159153 | T C    | 414 85 9 422 100 4 | 0.96 (0.63-1.46) 0.849 | 1.35 (0.28-6.56) 0.708 | 0.465 |
| hOGG1   | rs293795 | A G    | 472 36 0 460 65 1 | 0.63 (0.36-1.11) 0.111 | / | / | 0.407 |
| FEN1    | rs174538 | A G    | 155 275 78 176 240 110 | 1.04 (0.73-1.48) 0.841 | 0.71 (0.46-1.09) 0.114 | 0.095 |
| APEX1   | rs1130409 | T G    | 192 237 79 178 239 109 | 0.81 (0.57-1.14) 0.227 | 0.76 (0.50-1.16) 0.207 | 0.084 |
| APEX1   | rs1760944 | T G    | 185 238 85 186 239 101 | 1.04 (0.74-1.47) 0.805 | 0.93 (0.60-1.42) 0.718 | 0.125 |
| APEX1   | rs3136817 | T C    | 426 80 2 434 88 4 | 0.77 (0.50-1.20) 0.252 | 0.32 (0.02-6.67) 0.461 | 0.842 |
| LIG3    | rs1052536 | C T    | 255 199 54 249 234 43 | 1.07 (0.77-1.48) 0.707 | 1.70 (0.97-2.98) 0.063 | 0.243 |
| LIG3    | rs3744356 | C T    | 493 15 0 514 12 0 | 1.04 (0.38-2.84) 0.947 | / | / | 0.791 |
| LIG3    | rs4796030 | A C    | 145 259 104 164 259 103 | 1.39 (0.97-1.99) 0.076 | 1.12 (0.75-1.68) 0.586 | 0.967 |
| XRCC1   | rs1799782 | G A    | 251 216 41 272 214 40 | 1.06 (0.76-1.46) 0.745 | 1.15 (0.62-2.13) 0.663 | 0.815 |
| XRCC1   | rs25487  | C T    | 269 200 39 302 184 40 | 1.16 (0.83-1.61) 0.384 | 1.49 (0.80-2.75) 0.207 | 0.111 |
| XRCC1   | rs25489  | C T    | 420 83 5 409 113 4 | 0.84 (0.56-1.27) 0.407 | 2.94 (0.49-17.76) 0.241 | 0.205 |
| XRCC1   | rs2682585 | G A    | 371 132 5 393 118 15 | 1.23 (0.85-1.77) 0.273 | **0.21 (0.06-0.79)** **0.022** | 0.098 |
| XRCC1   | rs3810378 | G C    | 268 198 42 295 189 42 | 1.18 (0.85-1.63) 0.336 | 1.37 (0.76-2.49) 0.294 | 0.136 |
| XRCC1   | rs915927 | T C    | 378 126 4 395 120 11 | 1.13 (0.78-1.63) 0.529 | 0.35 (0.09-1.43) 0.144 | 0.597 |

Table 2. Association of polymorphisms in base excision repair pathway genes with allergic rhinitis susceptibility. OR, odds ratio; CI, confidence interval. HWE, Hardy-Weinberg equilibrium. *Adjusted for age and sex for dominant model. **Adjusted for age and sex for recessive model.
| Variables             | hOGG1 (95% CI) | AOR (95% CI) | p<sup>ab</sup> | LIG3 (95% CI) | AOR (95% CI) | p<sup>a</sup> | LIG3 (95% CI) | AOR (95% CI) | p<sup>a</sup> | XRCC1 (95% CI) | AOR (95% CI) | p<sup>a</sup> |  |
|----------------------|----------------|--------------|---------------|---------------|--------------|---------------|---------------|--------------|---------------|----------------|--------------|---------------|  |
|                      | rs1052133      |              |               | rs1052536     |              |               | rs4796030     |              | rs2682585     |                |              |               |  |
|                      | (cases/controls) |              |               | (cases/controls) |              |               | (cases/controls) |              | (cases/controls) |                |              |               |  |
|                      | GG             | GC/CC        | CC/CT         | TT            | AA           | AC/CC         | AA/AG         | GG           |               |                |              |               |  |
| Age, month           |                |              |               |               |              |               |               |              |               |                |              |               |  |
| ≤60                  | 69/123         |              | 95/299        |               |              |               |               |              |               |                |              |               |  |
| >60                  | 121/33         |              | 223/71        |               |              |               |               |              |               |                |              |               |  |
| Gender               |                |              |               |               |              |               |               |              |               |                |              |               |  |
| Females              | 104/72         |              | 153/169       |               |              |               |               |              |               |                |              |               |  |
| Males                | 86/84          |              | 165/201       |               |              |               |               |              |               |                |              |               |  |
| Severity grade       |                |              |               |               |              |               |               |              |               |                |              |               |  |
| Mild                 | 49/156         |              | 98/370        |               |              |               |               |              |               |                |              |               |  |
| Moderate             | 98/156         |              | 129/370       |               |              |               |               |              |               |                |              |               |  |
| Severe               | 43/156         |              | 91/370        |               |              |               |               |              |               |                |              |               |  |

Table 3. Stratification analysis for the association between base excision repair pathway gene variant genotypes and allergic rhinitis risk. CI, confidence interval; AOR, adjusted odds ratio.

*Obtained in logistic regression models with adjustment for age and sex omitting the corresponding stratification factor.
demonstrated that genomic instability also causes inflammatory responses. For instance, DNA damage could activate some transcription factors, such as NFκB and HMGB1, which are key regulatory factors for promoting the expression of downstream pro-inflammatory cytokines. BER system is important for maintaining the stability of the genome, and it is also mainly responsible for DNA damage repair during inflammation. Numerous studies have indicated that the BER core genes have vital roles in the progression of various inflammatory disorders. For example, pharmacological inhibition of PARP-1 activity or PARP-1 knockout could attenuate the inflammatory response. OGG1-deficient mice have a higher expression of pro-inflammatory cytokines, which causes an increased risk of intestinal inflammation.

SNPs in BER pathway genes may change the expression and activity of genes, which may lead to genetic instability and triggers inflammation eventually. Koc et al showed that heterozygosity of rs1136410 T > C in PARP-1 had a protective effect against Hashimoto’s thyroiditis in Turkish women, they also proved that heterozygous genotype of rs7527192 G > A in PARP-1 was significantly associated with AR risk. One study performed by da Silva et al revealed significant correlations between APEX1 rs1130409 T > G, hOGG1 rs1052133 G > C, PARP-1 rs1136410 T > C, and meningitis. In our study, we for the first time...
comprehensively explored whether SNPs in the BER core genes will modify the AR susceptibility. Detailed, hOGG1 rs1052133 GC/CC genotype significantly reduced AR risk compared with rs1052133 GG genotype; XRCC1 rs2682585 GG genotype decreased the AR risk significantly compared with rs2682585 AA/GA genotype. The stratified analysis further showed that hOGG1 rs1052133 GC/CC genotype reduced AR risk mainly in the following subgroups: age <60 months, females, and moderate AR; And XRCC1 rs2682585 GG genotype reduced the risk of AR in the subjects age >60 months. Moreover, LIG3 rs1052536 TT genotype increased the AR risk significantly in the patients with clinical severe AR compared with rs1052536 CC/CT genotype, which is a null association with AR risk in the single locus analysis, it may be just a chance finding on account of relatively small sample size in the stratified analysis.

In the BER, hOGG1, and XRCC1 play central roles in maintaining genome integrity. The rs1052133 G > C polymorphism was associated with the DNA repair capacity of hOGG1. The individuals with rs1052133 CC genotype have a two-fold higher capacity of DNA damage repair compared to those with rs1052133 GG genotype. The reduction of DNA repair capacity of hOGG1 may contributes to AR risk. The rs2682585 G > A was located at the promoter region of XRCC1 which may modify XRCC1 gene expression, which may affect the AR susceptibility.

To further explore the biological effects of these 2 associated SNPs on genes expression and the possible mechanisms by which the associated SNPs affect the AR risk, we performed the eQTL analysis. The results suggested that the rs1052133 G allele was related to an increased mRNA level of hOGG1, TTL3, and CRELD1. Previous study also indicated that an increase in the expression of hOGG1 could exacerbate the inflammatory response. However, the associations between TTL3, CRELD1, and AR risk, and the mechanism that rs1052133 G > C polymorphism affect the mRNA expression of TTL3 and CRELD1 are needed to be further explored. And regarding SNP rs2682585 G > A, the G allele was associate with the reduced mRNA expression of PINLYP and increased mRNA expression of ETHE1. This SNP-base expression change of neighboring genes may contribute to this rs1052133 G > C genotype-base AR risk. In this current study, despite in the preliminary stage, we provide new insights on how BER pathway genes variants affect the AR risk.

Several accompanying limitations in this study should be mentioned. First, the study sample size was relatively small, especially for stratified analysis. Second, the other potential functional SNPs should be assessed. Third, analysis of environmental factors should be included, as AR is a polygenic disease, which involves complex interactions between multiple environmental and genetic factors. Fourth, all subjects in this study are Chinese, maybe the conclusions drawn from this study will not suitable for other ethnicities. Fifth, functional experiments should be conducted to clarify the exact mechanism that variants of BER pathway genes modify the AR susceptibility.

CONCLUSIONS

In conclusion, this present research was the first case-control study to comprehensively assess the effects of genetic variants of BER core genes on AR risk. Our findings suggested that the genetic variants of hOGG1 and XRCC1 modified the AR susceptibility significantly in Chinese children. Well-designed studies with a large sample size collect from multiple centers are warranted to verify the conclusion.

Moreover, the underlying mechanisms that hOGG1 and XRCC1 genetic variants affect AR susceptibility should be revealed by a series of functional studies.

Abbreviations
AR, Allergic rhinitis; BER, base excision repair; SNPs, single nucleotide polymorphisms; eQTL, expression quantitative trait loci.

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Data availability statement
All data generated or analyzed during this study are included in this published article and its additional files.
Authors’ contributions
Study design: Wenlong Liu, Qingxiang Zeng; experiment: Qingxiang Zeng, Yinhui Zeng, Yiquan Tang; data collected and analysis: Wenlong Liu, Yinhui Zeng, Yiquan Tang; manuscript drafting: Wenlong Liu and Qingxiang Zeng.

Ethical statement
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. All participants have signed the informed consent by their guardians and the study protocol was approved by the institutional review board of Guangzhou women and children’s hospital (No. 126A01) before the study.

Consent for publication
The authors provide their consent for the publication of the study results.

Declaration of competing interest
The authors declare that they have no conflicts of interest.

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Not applicable.

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