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# Genetic Single Nucleotide Polymorphisms (GSNPs) in the DNA Repair Genes and Hepatocellular Carcinoma Related to Aflatoxin B1 among Guangxiese Population

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Xue-Ming Wu, Zhi-Feng Xi, Jun Lu, Xing-Zhizi Wang, Tian-Qi Zhang, Xiao-Ying Huang, Jin-Guang Yao, Chao Wang, Zhong-Heng Wei, Chun-Ying Luo, Bing-Chen Huang, Qun-Qing Xu, Wen-Pei Yang, Qiang Xia and Xi-Dai Long

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## Abstract

Aflatoxin B1 (AFB1) is an important environmental carcinogen for the development of hepatocellular carcinoma (HCC). HCC is a complex disease likely resulting from genetic single nucleotide polymorphisms (GSNPs) of multiple interacting genes and gene-environment interactions. Recent efforts have been made to analyze the associations between risk of this malignancy and GSNPs in genes involved in the repair of DNA damage induced by AFB1. Here, we reviewed the results of published case-control studies that have examined the effects of common alleles of all susceptible DNA repair genes, including XRCC1, XRCC3, XRCC4, XRCC7, XPC, and XPD, on risk of AFB1-related HCC among Guangxi population. Statistically significant differences in genotype frequencies found in case-control comparisons were rs25487, rs80309960, rs861539, rs7003908, rs28383151, rs3734091, rs13181, and rs2228001 polymorphism. The overall effects of these GSNPs were moderate in terms of relative risk, with ORs ranging from 2 to 10. Furthermore, some evidence of the interaction of GSNPs in DNA repair genes and AFB1 exposure modulate risk of this cancer was also found, although the results require confirmation with larger sample size studies.

**Keywords:** genetic single nucleotide polymorphism, hepatocellular carcinoma, DNA repair, DNA damage, aflatoxin B1, Guangxiese population

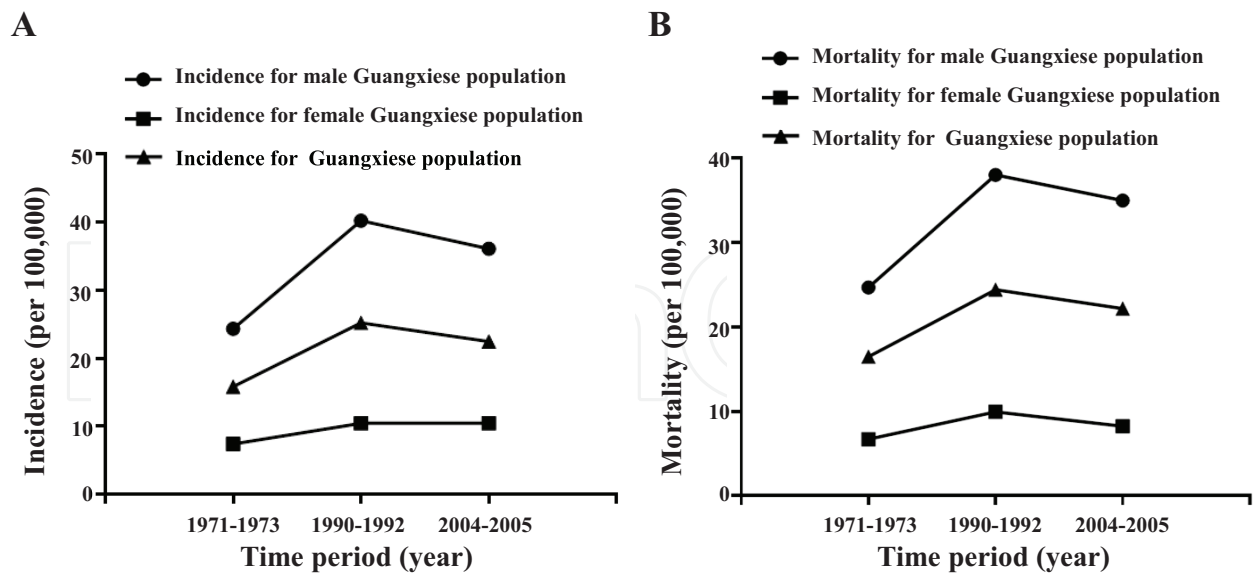
## 1. Introduction

In China, hepatocellular carcinoma (HCC) is the fourth most common malignant tumors and accounts for about 50% of the world's HCC cases [1, 2]. This malignancy occurs more often in some hot and humid areas such as Guangxi area, mainly because of high aflatoxin B1 (AFB1) exposure [3, 4]. However, accumulating epidemiological evidence has shown that although many people are exposed to this risk factor, only a relatively small proportion of people with chronic AFB1 exposure develop HCC [3, 4]. This suggests that an individual susceptibility related to genetic factors including genetic single nucleotide polymorphisms (GSNPs) in DNA repair genes might be correlated with HCC tumorigenesis [3–5]. In past several decade years, evidence has been accumulated to support the hypothesis that GSNPs in DNA repair genes may be of importance in determining individual susceptibility to AFB1-related HCC [6–8]. Here, we review recent efforts in identifying genetic single nucleotide polymorphisms (SNPs) in DNA repair genes, which may have impact on AFB1-related HCC risk among Guangxi population.

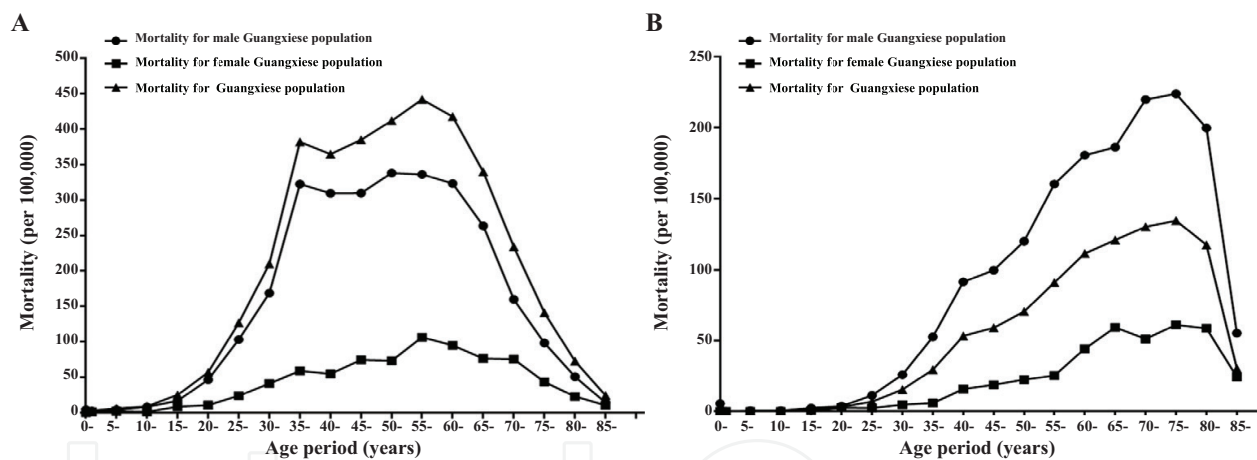
## 2. Epidemiology of AFB1-related HCC among Guangxi areas

In Guangxi, a known high AFB1 exposure area, HCC is the most common occurring cancer [5]. Epidemiologically, this type tumor is characterized as follows: (a) the incidence rate displaying a noticeable mountain shape, gradually increasing with age increasing before shape top and gradually decreasing with age increasing after shape top and (b) more than three times risk of HCC among males than among females, especially in the high AFB1-exposure areas (including Baise and Nanning) [5]. During 1990–1992, the incidence rates of this tumor in Guangxi area increased markedly compared between the late 1970s and the early 1980s (25.22 per 100,000 vs. 15.85 per 100,000), especially male Guangxi population (**Figure 1A**) [9]. This might result from the increasing infective rate of hepatitis viruses and advance of diagnostic ability [10]. The following epidemiological investigations showed that the incidence rate of HCC among Guangxi population significantly decrease during 2004 and 2005 (mainly because of the control of hepatitis virus infection) (**Figure 1**) [9]. However, the incident rates of this tumor in high AFB1-exposure areas have little change. According to epidemiological investigation from AFB1-exposure areas, during May 2007–April 2008, incidence rates were 103.1/100,000 and 117.8/100,000 for Fusui in Nanning and Xiangzhou in Baise (two main high AFB1 exposure areas), respectively [11]. This is similar to the results before 10 years [11].

Because of the very poor prognosis, HCC is the first most common cause of death from cancer in Guangxi [9]. In the past 40 years, the total mortality rate of HCC gradually increased and followed by gradually decreased (**Figure 1B**), regardless of male or female population. Furthermore, this trend was not only associated with age but also more noticeable in male population than female population (**Figure 2**), possibly because male individuals featured more AFB1 exposure [4]. Supporting above-mentioned hypothesis, molecular epidemiological studies from high AFB1-exposure areas of Guangxi have exhibited that these individuals featuring more AFB1 exposure would face decreasing 5-year survival rate and increasing death risk [12–14].



**Figure 1.** The incidence and mortality rates of hepatocellular carcinoma (HCC) in Guangxi during 1971 and 2005. Total incidence rate (A) and mortality rates (B), regardless of male or female population, were significantly increasing from during 1971 and 1973 to during 1990 and 1992. However, they would decrease during 2004 and 2005.



**Figure 2.** The gender and age distributions of hepatocellular carcinoma (HCC) mortality among Guangxi population. (A) The gender and age distributions of HCC mortality between 1990 and 1992. (B) The gender and age distributions of HCC mortality between 2004 and 2005.

### 3. DNA damage induced by AFB1 and DNA repair

Several previous reviews have significantly summarized the toxicology of AFB1 [3–5, 15]. Generally, AFB1, an important mycotoxin and a category I known human carcinogen produced by *Aspergillus parasiticus* and *Aspergillus flavus* [4, 5], has been found as toxic contaminants of human food such as ground nuts and core in tropical areas as a result of fungal contamination during growth and after harvest which under hot and humid conditions [15]. Once this toxigenic agent is taken into body, it is metabolized by phase I detoxification enzymes to its reactive form, also called AFB1-8,9-epoxide (AFBO). This reactive product can

also covalently bind to DNA and induce DNA damage, which might ultimately result to the development of HCC [16, 17].

AFB1-induced DNA damage types consist of DNA adducts, oxidative damage, and gene mutations. For AFB1-DNA adducts, AFB1-N<sup>7</sup>-Gua adduct, the most common adduct type, is primarily identified and confirmed *in vivo* research studies [17–22], whereas the formamidopyridine AFB1 adduct (AFB1-FAPy) is a ring-opened DNA adduct [23, 24]. Because of the accumulations of AFB1-FAPy, it is characterized by a time-dependent and non-enzyme way and exhibits apparent persistence in DNA; it may be of biological basis of genes mutation. Furthermore, AFB1-N<sup>7</sup>-Gua and AFB1-FAPy can induce error-prone DNA repair and result in the damage of DNA strands, including double-strand breaks (DSBs), single-strand breaks (SSBs), base pair substitution, frame shift mutations, and oxidation DNA damage such as 8-oxodeoxyguanosine (8-oxoG) [25–28]. For genes mutations induced by AFB1 exposure, G:C > T:A mutation in codon 249 of TP53 gene has been frequently reported [29–36]. This mutation is tested in more than 40% of HCC from high-AFB1-exposure areas, but in either very rare or absent for those from low or null AFB1 exposure areas [36–39]. Therefore, G:C > T:A mutation in codon 249 of TP53 gene is regarded as the hotspot mutation caused by AFB1 and the molecular symbol of AFB1-related HCC [40–42].

DNA damage by AFB1 exposure, if not repaired, may cause genomic instability and ultimately result in cellular malignant transformation and tumor formation [20]. In human cells, several evolved surveillance mechanisms, including base excision repair (BER), nucleotide excision repair (NER), single-strand break repair (SSBR), and double-strand break repair (DSBR), can monitor the integrity of genome and repair and minimize the consequences of detrimental genome damage [3, 40]. DNA repair genes play an important role during aforementioned repair pathways of DNA damage; therefore, GSNPs in the DNA repair genes may be associated with risk of developing AFB1-related HCC [4].

#### 4. Xeroderma pigmentosum C (XPC) GSNPs and AFB1-HCC among Guangxi population

Xeroderma pigmentosum C (XPC) gene locates on chromosome 3p25 and spans 33kb. Its encoding protein consists of 940 amino acids and acts as a DNA damage recognition molecule during the global genome NER pathway [43, 44]. XPC can bind tightly with RAD23 homolog B (RAD23B, also called HR23B) to form a stable XPC/RAD23B complex. This complex can recognize DNA adducts formed by exogenous carcinogens such as AFB1 and binds to the DNA damage sites [44]. Thus, XPC may play a role in the pathogenesis of HCC-related AFB1. The pathological and cellular researches have shown that the abnormal expression of this gene is correlated with hepatocarcinogenesis [45]. Some studies have shown that GSNPs of XPC (rs2228001 (also called codon Lys939Gln polymorphism) can decrease DNA repair capacity related to AFB1-induced DNA damage [46–49]. In the past several decade years, a total of four studies from Guangxi area reported XPC rs2228001 polymorphism was involved in AFB1 detoxification (**Table 1**) [12, 49–51]. The first study

No.	Ref.	Year	AFB1 exposure <sup>a</sup>	Methods	Matching factor	Cases	Controls	Risk value <sup>b</sup>
						(n)	(n)	(OR)
1	Wu et al. [51]	2010	High	Case-control	Age, sex, HBV, HCV, race	98	157	1.46–2.08 ( <i>P</i> < 0.05)
2	Long et al. [12]	2010	High	Case-control	Age, sex, HBV, HCV, race	1156	1402	1.25–1.81 ( <i>P</i> < 0.001)
3	Li et al. [50]	2010	High	Case-control	No	500	507	1.20–1.81 ( <i>P</i> > 0.05)
4	Yao et al. [49]	2014	High	Case-control	Age, sex, HBV, HCV, race	1486	1996	1.57–2.19 ( <i>P</i> < 0.001)

<sup>a</sup>Defined by means of Henry et al. (Science, 1999).

<sup>b</sup>AFB1-related HCC risk will increase if OR > 1 and corresponding *P*-value < 0.05; will decrease if OR < 1 and corresponding *P*-value < 0.05; and will not change if OR is about 1 and/or corresponding *P*-value > 0.05.

**Table 1.** Characteristics of studies about GSNP at codon 939 of XPC and AFB1-related HCC risk.

conducted by Wu et al. [51] is from Baise area (a famous high AFB1 exposure area with high incidence rate of HCC). In this study, researchers investigated the association between XPC rs2228001 polymorphism and HCC risk via an hospital-based case-control study (including 98 HCC patients and 157 age-, sex-, race-, and hepatitis viruses-matching controls) method and found XPC rs2228001 polymorphism increased HCC risk of female individuals (odds ratios [ORs] were 5.44 with 95% CI 1.38–21.50), but not tumor risk of male population. Noticeably, they found a significant interaction of XPC variables and AFB1 exposure levels [51].

Results from the matching-design studies with large-size samples show that the mutant genotypes of XPC rs2228001 polymorphism increased about two times risk of HCC [12, 49]. The following quantitative analysis exhibited that AFB1 exposure interacted with risk genotypes of XPC rs2228001 polymorphism on HCC risk ( $22.33 > 1.88 \times 8.69$  for the interaction of AFB1-exposure years and XPC risk genotypes and  $18.38 > 1.11 \times 4.62$  for the interaction of AFB1-exposure levels and XPC risk genotypes) [12, 49]. Furthermore, mutant alleles were correlated with the decrease of XPC expression levels in cancerous tissues and with the overall survival of HCC patients [12]. However, another study also from Nanning area (another high AFB1 exposure area in Guangxi) exhibited that this polymorphism does not change HCC risk [50], possibly because it bases on nonmatching design and some confounders might affect their results. Interestingly, a significant risk value for HCC among female population was observed in the stratified analyses (OR = 2.17, 95% CI = 1.01–4.64), similar with findings from Wu et al. [51]. Given these different effects, we accomplished meta-analysis and found XPC rs2228001 polymorphism increased AFB1-related risk (combined OR = 1.89, *P* < 0.01). Therefore, these results demonstrate that GSNP at codon 939 of XPC gene is not only a genetic determinant in the development of HCC caused by AFB1

in Guangxiese population but also an independent prognostic factor influencing the survival of HCC, like AFB1 exposure.

## 5. Xeroderma pigmentosum D (XPD) GSNPs and AFB1-HCC among Guangxiese population

Xeroderma pigmentosum gene, contains 22 introns and 23 exons, locates on 19q13.3 and spans about 20 kb [3, 52]. Its encoded product is one of the TFIIH complexes (a DNA-dependent ATPase/helicase complex), it has classically been linked to the damage verification and the opening of the DNA helix step of NER pathway [53]. To date, molecular epidemiological studies on two GSNPs in this gene, namely, rs369191500 polymorphism (codon 312, Asp to Asn) and rs13181 polymorphism (codon 751, Lys to Gln), have been conducted by different laboratories [54]. Genotype-phenotype analyses have shown that these two GSNPs are associated with low DNA repair ability, which might modify DNA-adduct levels, p53 gene mutation, and risk of cancer [55, 56]. For genetic polymorphisms among Guangxiese population, a total of four epidemiological studies have been conducted via case-control design (Table 2). In 2009, Zeng et al. [57] investigated the association between XPD GSNPs and HCC and observed about 2.60-time risk of HCC for these with mutant genotypes of XPD codon 751. After that, results from Long et al. [58] and Yao et al. [49] have exhibited that the variants of XPD rs13181 polymorphism (including rs13181-LG and -GG) was significantly different between controls and HCC cases (26.3 vs. 35.9% for rs13181-LG and 8.6 vs. 20.1% for rs13181-GG, respectively,  $P < 0.001$ ). Mutant alleles increased the

No.	Ref.	Year	AFB1 exposure <sup>a</sup>	Methods	Matching factor	Cases (n)	Controls (n)	Risk value <sup>b</sup> (OR)
1	Zeng et al. [57]	2009	High	Case-control	No	300	312	About 2.60 ( $P < 0.001$ )
2	Long et al. [58]	2009	High	Case-control	Age, sex, HBV, HCV, race	618	712	1.75–2.47 ( $P < 0.001$ )
3	Yao et al. [49]	2014	High	Case-control	Age, sex, HBV, HCV, race	1486	1996	2.19–4.27 ( $P < 0.001$ )
4	Hu et al. [59]	2016	High	Case-control	No	178	178	2.33–3.38 ( $P < 0.05$ )

<sup>a</sup> Defined by means of Henry et al. (Science, 1999).

<sup>b</sup> AFB1-related HCC risk will increase if  $OR > 1$  and corresponding  $P$ -value  $< 0.05$ ; will decrease if  $OR < 1$  and corresponding  $P$ -value  $< 0.05$ ; and will not change if  $OR$  is about 1 and/or corresponding  $P$ -value  $> 0.05$ .

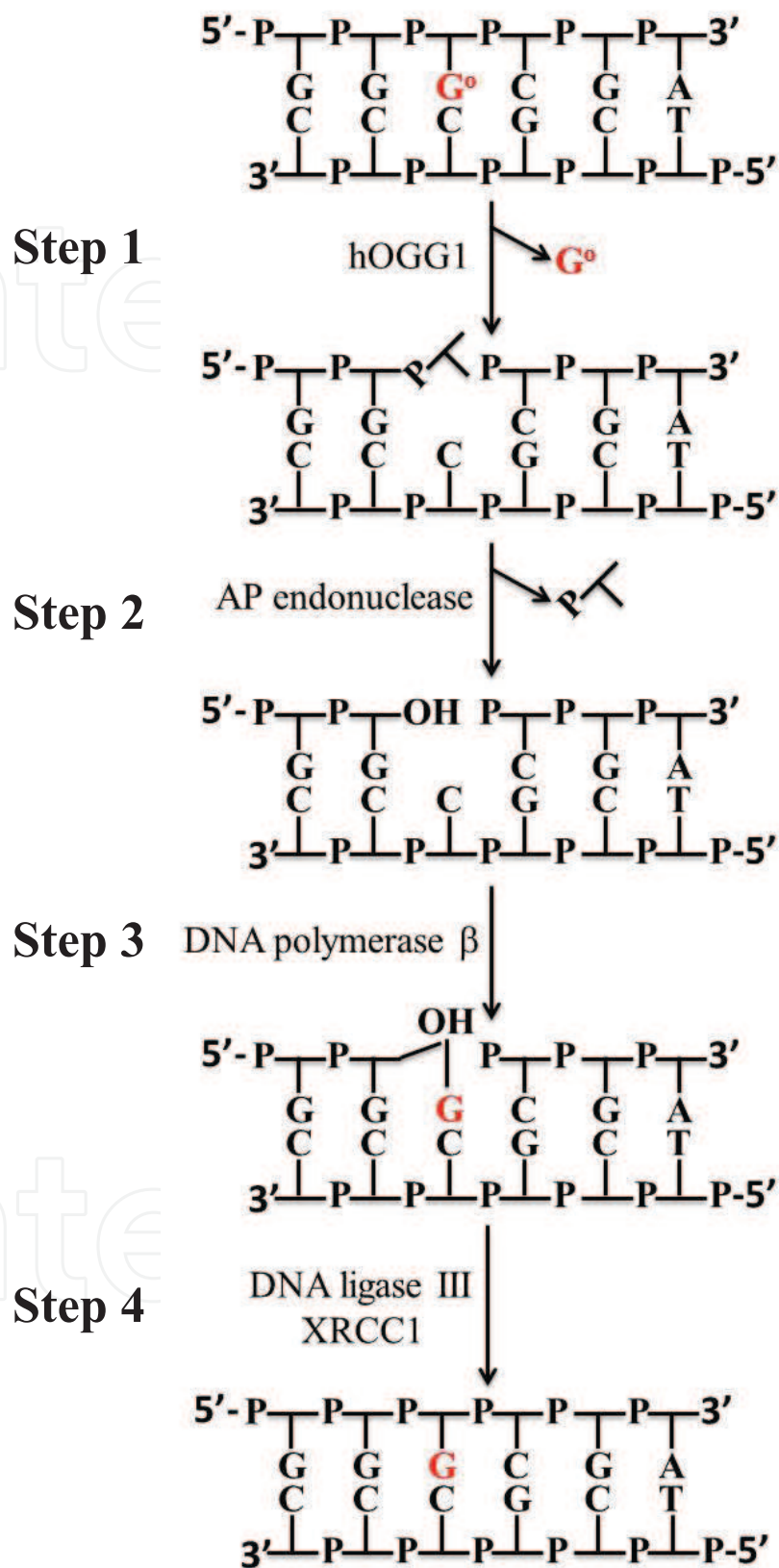
**Table 2.** Characteristics of studies about genetic polymorphism at codon 751 of XPD and AFB1-related HCC risk.

risk of developing the cancer with a risk value of 1.75 (1.30–2.37) for Lys/Gln and 2.47 (1.62–3.76) for Gln/Gln, respectively [58]. Furthermore, the interactive effects of mutant genotypes of rs13181 polymorphism in XPD gene and AFB1 exposure on HCC risk were also found ( $P_{\text{interaction}} < 0.05$ ) [49]. Recently, Hu et al. [59] have reported higher frequency of XPD codon 751 Gln alleles among HCC families than among non-HCC families. This suggests that genetic susceptibility resulting from XPD GSNPs might have a potential effect on AFB1-related HCC risk among Guangxi population. Meta-analysis further improved the above-mentioned hypothesis [56]. However, the studies from molecular epidemiological studies exhibit that another GSNP of XPD is not significantly correlate with the risk of HCC related to AFB1 [49, 58].

## 6. The human 8-oxoguanine DNA glycosylase (hOGG1) GSNPs and AFB1-HCC among Guangxi population

As described previously [60], DNA glycosylases play a central role in the BER pathway because they can recognize and catalyze the removal of damaged bases. Among having been reported GSNPs in DNA glycosylase-encoded genes, only hOGG1 correlates with DNA repair capacity [5, 61]. This gene consists of 7 exons and 6 introns and spans 17 kb on chromosome 3p26.2. It encodes a 546-amino acid protein, a specific DNA glycosylase that catalyzes the release of 8-<sub>oxy</sub>G and the cleavage of DNA at the AP site (**Figure 3**) [61, 62]. The presence of several polymorphisms within hOGG1 locus is identified and only rs1052133 polymorphism (at codon 326, Ser → Cys) is suggested to modify DNA repair capacity [63–65]. Therefore, low capacity of 8-<sub>oxy</sub>G repair resulting from hOGG1 326Cys polymorphism might contribute to the persistence of 8-<sub>oxy</sub>G in genomic DNA *in vivo*, which, in turn, could be associated with increased cancer risk [66]. Several reports imply this polymorphism may be associated with HCC related to AFB1 exposure [67–70]. Through a hospital-based case-control study (including 500 cases with HCC and 507 healthy controls) conducted in Nanning area from Guangxi, Ji et al. [67] investigated the relationship between hOGG1 rs1052133 polymorphism and HCC risk and found significantly different distribution of three genotypes (Ser/Ser, Ser/Cys, and Cys/Cys) between cases and controls (71.40, 8.00, and 20.60% for patients with HCC, 84.22, 10.06, and 5.72% for controls). Regression logistic analysis shows that mutant alleles of this polymorphism increase AFB1-related HCC risk (OR = 2.14, 95% CI = 1.57–2.91). Molecular epidemiological studies from other researchers have also proved higher frequencies of Cys alleles in HCC cases than controls and this change increased HCC risk among Guangxi population featuring AFB1-exposure history [69, 70]. Given that hOGG1 expression is significantly related to HCC carcinogenesis [71, 72], Peng et al. [68] explored the effects of hOGG1 rs1052133 polymorphism on 8-<sub>oxy</sub>G levels and hOGG1 expression in Guangxi population with AFB1 exposure. They observed that Cys alleles downregulated hOGG1 expression and increased 8-<sub>oxy</sub>G levels. These findings suggested the pathogenic role of hOGG1 Cys326Ser polymorphism in the carcinogenesis of AFB1-related HCC.





**Figure 3.** The base excision repair for oxidative DNA damage 8-oxoG in mammalian cells. In this repair pathway, human 8-oxoguanine DNA glycosylase (hOGG1) can catalyze the release of 8-oxoG (Red) and the cleavage of DNA at the AP site.

## 7. The XRCC1 GSNPs and AFB1-HCC among Guangxiese population

X-ray repair cross-complementing group 1 (XRCC1), also called RCC, spans about 32 kb on chromosome 19q13.2 and contains 17 exons and 16 introns. The encoding protein of XRCC1 acts as a scaffold protein in SSBR and BER pathways via the interaction with Pol  $\beta$ , DNA ligase III, and PARP [73]. According to data from SNP database, more than 50 GSNPs in the coding region of XRCC1 gene, which lead to amino acid substitution, have been identified. Of GSNPs, rs25487 polymorphism (at codon 399, Arg  $\rightarrow$  Gln) is of special concern, because this GSNP resides in functionally significant regions and may decrease DNA repair activity and increase the risk of gene mutation cancers [3].

In Guangxi area, a total of five molecular epidemiological studies were found in PubMed Database, Web of Science Database, Wangfang Database, Google Database, and Weipu database (**Table 3**). In 2005, Long et al. [74] investigated the effects of XRCC1 rs25487 polymorphism on AFB1-related HCC risk. In their study, they included 140 patients with pathologically diagnosed HCC and 536 age-, sex-, race-, and hepatitis virus-matching controls and found significantly different distribution of three genotypes of XRCC1 rs25487 polymorphism (Arg/Arg, Arg/Gln, and Gln/Gln) between cases and controls (51.43, 45.00, and 3.57% for patients with HCC, 6.54, 29.66, and 2.88% for controls). Regression logistic analysis shows that mutant alleles of this polymorphism increase AFB1-related HCC risk (OR = 2.18, 95% CI = 1.27–3.74). They also observed more noticeable risk role for HCC under the conditions of individuals with both high AFB1 exposure and mutant genotypes of XRCC1 rs25487 polymorphism (risk value 1.84–10.87). The several following molecular epidemiological studies furthermore prove these results [49, 75, 77]. However, associations between

No.	Ref.	Year	AFB1 exposure <sup>a</sup>	Methods	Matching factor	Cases (n)	Controls (n)	Risk value <sup>b</sup> (OR)
1	Long et al. [74]	2005	High	Case-control	Age, sex, HBV, HCV, race	140	536	2.18 (P = 0.0001)
2	Long et al. [75]	2006	High	Case-control	Age, sex, HBV, HCV, race	257	649	2.47 (P = 0.0001)
3	Zeng et al. [76]	2010	High	Case-control	No	500	507	about 1 (P > 0.05)
4	He et al. [77]	2012	High	Case-control	Age, sex	119	119	2.50 (P < 0.05)
5	Yao et al. [49]	2014	High	Case-control	Age, sex, HBV, HCV, race	1486	1996	2.19–4.27 (P < 0.001)

Notes: <sup>a</sup> Defined by means of Henry et al. (Science, 1999, 286: 2453-2454).

<sup>b</sup> AFB1-related HCC risk will increase if OR > 1 and corresponding P-value < 0.05; will decrease if OR < 1 and corresponding P-value < 0.05; and will not change if OR is about 1 and/or corresponding P-value > 0.05.

**Table 3.** Characteristics of studies about genetic polymorphism at codon 399 of XRCC1 and AFB1-related HCC risk.

XRCC1 rs25487 polymorphism and individual susceptibility to HCC have been reported in a case-control study with the insignificant results [76]. This may be because of nonmatching design and the effects of confounders such as age, gender, race, and hepatitis viruses. Supporting aforementioned conclusions, meta-analysis from data in high AFB1 exposure areas also exhibited that these subjects with Gln alleles of XRCC1 rs25487 polymorphism had increasing HCC risk (OR > 1,  $P < 0.01$ ) [78]. This suggests that XRCC1 rs25487 polymorphism should be a risk biomarker of Guangxiese HCC related to AFB1 exposure.

## 8. The XRCC3 GSNPs and AFB1-HCC among Guangxiese population

X-ray repair cross-complementing group 3 (XRCC3) is an important paralog of the strand-exchange protein RAD51 and is primarily found and cloned by functional complementation in the Chinese hamster cell line irs1SF. This gene spans about 17.8 kb on chromosome 14q32.33 and contains 10 exons. Functionally, XRCC3 can bind directly with DNA breaks and facilitate the formation of the RAD51 nucleoprotein filament and protein-protein interaction of RAD51 family members in the SSBR pathway [79]. In XRCC3-defective irs1SF hamster cells, spontaneous chromosomal aberrations, high sensitivity to cross-linking agents, mild sensitivity to gamma rays, and significantly attenuated Rad51 focus formation after gamma ray exposure were observed, which suggests that XRCC3 is crucial for the SSBR pathway [80].

Recent molecular epidemiological studies have shown that the function of XRCC3 is modified by its GSNPs. Of the known GSNPs, only rs2228001 polymorphism (at codon 241, Thr → Met) is of special concern, because this GSNP results the change Thr to Met at codon 241 [81–83]. Up to now, three reports from high AFB1-exposure areas of Guangxi supported the above-mentioned conclusions [49, 84, 85]. In the first frequent case-control study in Guangxi population [85], higher mutant frequencies at codon 241 of XRCC3 are observed among cases with HCC than controls (33.01 vs. 61.48%,  $P < 0.001$ ). The results from logistic regression analysis further prove that this mutate increases about 2- to 10-time risk of HCC. The following two relatively larger sample size molecular epidemiological studies (study 1 conducted by Long et al. [84] consisting of 491 patients with HCC and 862 healthy controls; study 2 from Yao et al. [49] including 1486 cases and 1996 controls) were accomplished in high AFB1 exposure. Similar to data from the first study, individuals having the mutant genotypes of XRCC3 rs2228001 polymorphism would feature higher risk of developing HCC. Interactive analysis of risk genotypes and AFB1 exposure further demonstrated that this allele multiplicatively interacted with AFB1 exposure in the process of hepatotumorigenesis [49]. Taken together, these results suggest that the GSNPs in XRCC3 gene, such as rs2228001 polymorphism, might a genetic determinant in the HCC carcinogenesis caused by AFB1 exposure among Guangxiese population.

## 9. The XRCC7 GSNPs and AFB1-HCC among Guangxiese population

X-ray repair cross-complementing 7 (XRCC7), also called protein kinase DNA-activated catalytic polypeptide (PRKDC), spans about 197 kb on 8q11.21 and contains 85 exons. Protein

encoded by his gene is a member of the PI3/PI4-kinase family and acts as the catalytic subunit of the DNA-dependent protein kinase (DNA-PK). Functionally, it interacts with the Ku70/Ku80 heterodimer protein in the nonhomologous end joining (NHEJ) repair and recombination [86–88]. More than 200 of GSNPs have been reported in the XRCC7 gene, some of which are reported to affect tumorigenesis of malignant tumors [89–93]. In Guangxi area, several reports imply XRCC7 rs7003908 polymorphism (T to G) may be associated with HCC related to AFB1 exposure [49, 94]. Through a hospital-based case-control study (including 348 cases with HCC and 597 age-, gender-, race-, and hepatitis viruses-matched healthy controls) conducted in high AFB1 exposure area from Guangxi, Long et al. [94] investigated the association between XRCC7 rs7003908 polymorphism and HCC risk and found significantly different distribution of three genotypes (rs7003908-TT, -TG, and -GG) between cases and controls (25.9, 44.5, and 29.6% for patients with HCC, 58.1, 30.0, and 11.9% for controls). Regression logistic analysis shows that mutant alleles of this polymorphism increase AFB1-related HCC risk, with risk value of 3.45 (2.40–4.94) for rs7003908-TG and 5.04 (3.28–7.76) for rs7003908-GG, respectively. Furthermore, this GSNP was also related to higher the amounts of DNA adducts induced by AFB1 ( $r = 0.142$ ) [94]. Interestingly, it also multiplicatively interacts with AFB1-exposure variable (interactive value: OR = 1.74; 95% CI = 1.66–1.82;  $P = 2.21 \times 10^{-133}$ ) [49]. Taken together, these data exhibited that the XRCC7 rs7003908 polymorphism might modify AFB1-related HCC risk via decreasing NHEJ capacity. However, more studies are inquired to support this conclusion.

## 10. The XRCC4 GSNPs and AFB1-HCC among Guangxi population

X-ray repair cross-complementing 4 (XRCC4, also known as SSMED) is an important NHEJ pathway gene locating on 5q14.2 and spanning about 293 kb. This gene is a generally expressed protein of 334 amino acids residues and functions together with DNA ligase IV and DNA-PK in the repair of DNA double-strand breaks. XRCC4 plays an important role in both nonhomologous end joining and the completion of V(D)J recombination [95, 96]. Increasing evidence has shown that mutations in XRCC4 can cause short stature, microcephaly, and endocrine dysfunction (SSMED) resulting from more-deficient NHEJ capacity [97, 98]. This suggests that the low repair capacity of this gene from genetic changes might be associated with cancer risk [99, 100]. Up to now, only two GSNPs in the XRCC4 gene, namely, rs28383151 (at codon 56, Ala to Thr) and rs3734091 (at codon 247, Ala to Ser), have reported to be correlated with risk of AFB1-related HCC among Guangxi population [13, 14, 49]. In these studies, Long et al. [13, 14] have examined the association between genetic polymorphisms (Ala56Thr and Ala247Ser) in XRCC4 and risk of HCC in a large case-control study in at-risk Guangxi population. Genotypes were determined in 1499 patients with HCC and 2045 individually matched controls. We observed that individuals with Thr/Thr genotype at Arg194Trp site and Ser/Ser genotype at Ala247Ser site of XRCC4 had about twofold and threefold increased risk for the cancer compared with wild types, respectively. Furthermore, when risk genotypes of XRCC4 and AFB1-exposure were combined, this risk role was more noticeable, with the adjusted OR being 11.26 (95% CI, 8.36–15.18) for rs28383151 polymorphism and 14.43 (95% CI, 7.98–26.09) for rs3734091 polymorphism, respectively. Interactive analysis further exhibited this multiplicative interaction (interactive OR = 1.64, 95% CI = 1.55–1.73,  $6.41 \times 10^{-73}$ ) [49].

Functional exploration showed that these two polymorphisms increased AFB1-DNA adducts levels and TP53M risk, and AFB1-related HCC prognosis, suggesting they should be important modified factors of AFB1 toxicological effects [5, 13, 14]. Together, these results imply that XRCC4 rs28383151 and rs3734091 polymorphisms might play a role in the carcinogenesis of the liver under the conditions of AFB1 exposure.

## 11. Future directions

In the past decades, great progress has been made in understanding the molecular mechanisms of the GSNPs affecting risk of AFB1-related HCC. However, we are still far from a comprehensive view of this effect. The molecular mechanism about GSNPs in the DNA repair genes modifying the risk of HCC caused by AFB1 remains largely unknown. Although several reports have displayed that GSNPs may progress tumorigenesis of AFB1-related HCC via downregulating expression of DNA repair genes, breaking the structure of DNA repair proteins, or decreasing the function of DNA repair genes, more direct evidence is still missing. Disclosing the roles of different phenotypes of DNA repair genes will greatly benefit our understanding of pathological mechanisms of GSNPs affecting AFB1-related HCC risk, and will shed important light on the prevention values for individuals with risk types.

## 12. Conclusion

Like most other human cancers, HCC is a complex disease attributed to environment variation and genetic susceptible factors. In high incidence areas of HCC in Guangxi, AFB1 is an important environment variation. In the process of AFB1 hepatocarcinogenesis, DNA damage induced by AFB1 exposure plays a central role because of their genotoxicity and interactions with genetic susceptible factors. Numerous studies reviewed in this chapter have demonstrated that the hereditary variations in DNA repair genes (including XRCC1, XRCC3, XRCC4, XRCC7, hOGG1, XPC, and XPD) are related to the susceptibility to AFB1-related HCC among Chinese population. These molecular epidemiological studies have significantly contributed to our knowledge of the importance of genetic polymorphisms in DNA repair genes in the etiology of HCC related to AFB1 exposure. It would be expected that genetic susceptibility factors involved in DNA repair genes for HCC could serve as useful biomarkers for identifying at-risk individuals and, therefore, targeting prevention of this malignant tumor.

However, there are several issues to be noted. Because of conflicting data existing in the same ethnic population in view of between some genotypes of DNA repair genes and the risk of HCC related to AFB1, the conclusions should first be drawn carefully. For example, whether the XRCC1 Arg399Gln polymorphism is a risk factor or not remains controversial and further studies are needed. Second, because of the difference in population frequencies corresponding to genetic polymorphisms that depend on ethnicity, caution should be taken, particularly in extrapolating these data to other ethnic populations, especially from other high AFB1-exposure areas. Third, when risk of a specific polymorphism is considered, AFB1 exposure should be

stressed because AFB1 exposure may differ from areas to areas and from individuals to individuals. Last, in view of that fact the development of AFB1-related HCC is “polygenic,” a panel of susceptible biomarkers are warranted to define individuals at high risk for this cancer.

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## Abbreviations

8- <sub>oxy</sub> G	8-oxodeoxyguanosine
AFB1	aflatoxin B1
AFBO	AFB1-8,9-epoxide
AFB1-FAPy	8,9-dihydro-8-(2,6-diamino-4-oxo-3,4-dihydropyrimid-5-yl formamide)-9-hydroxy-AFB1
AFB1-N <sup>7</sup> -Gua	(8,9-dihydro-8-N <sup>7</sup> -guanyl-9-hydroxy-AFB1)
BER	base excision repair
DSBR	double-strand break repair
DSBs	double-strand breaks
GSNP	genetic single nucleotide polymorphism
HCC	hepatocellular carcinoma
HR	hazard ratio
hOGG1	human 8-oxoguanine DNA glycosylase
NER	nucleotide excision repair
NHEJ	nonhomologous end joining
OR	odds ratio
SSBs	single-strand breaks
SSBR	single-strand break repair
SSMED	short stature, microcephaly, and endocrine dysfunction

TP53M	the hotspot mutation at codon 249 of TP53 gene;
XPC	xeroderma pigmentosum C
XPD	xeroderma pigmentosum D
XRCC1	X-ray repair cross-complementing group 1
XRCC3	X-ray repair cross-complementing group 3
XRCC4	X-ray repair cross-complementing group 4
XRCC7	X-ray repair cross-complementing group 7

## Author details

Xue-Ming Wu<sup>1†</sup>, Zhi-Feng Xi<sup>2†</sup>, Jun Lu<sup>2†</sup>, Xing-Zhizi Wang<sup>1†</sup>, Tian-Qi Zhang<sup>1†</sup>, Xiao-Ying Huang<sup>1†</sup>, Jin-Guang Yao<sup>1†</sup>, Chao Wang<sup>3†</sup>, Zhong-Heng Wei<sup>4†</sup>, Chun-Ying Luo<sup>1†</sup>, Bing-Chen Huang<sup>1†</sup>, Qun-Qing Xu<sup>5†</sup>, Wen-Pei Yang<sup>6†</sup>, Qiang Xia<sup>2\*</sup> and Xi-Dai Long<sup>1,2\*</sup>

\*Address all correspondence to: [sjtuolongxd@263.net](mailto:sjtuolongxd@263.net) or [xiaqiang@sjtu.edu.cn](mailto:xiaqiang@sjtu.edu.cn)

1 Department of Pathology, the Affiliated Hospital of Youjiang Medical College for Nationalities (AHYMCN), Baise, China

2 Department of Liver Surgery, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

3 Department of Medicine, AHYMCN, Baise, China

4 Department of Tumor, AHYMCN, Baise, China

5 Department of Central Test, Youjiang Medical College for Nationalities, Baise, China

6 Department of Basic Medicine, Youjiang Medical College for Nationalities, Baise, China

† These authors contributed equally to this work.

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