Association between NER Pathway Gene Polymorphisms and Wilms Tumor Risk

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Nucleotide excision repair (NER) is an essential mechanism of the body to defend against exogenous carcinogen-induced DNA damage. Defects in NER may impair DNA repair capacity and, therefore, increase genome instability and cancer susceptibility. To explore genetic predispositions to Wilms tumor, we conducted a case-control study totaling 145 neuroblastoma cases and 531 healthy controls. We systematically selected 19 potentially functional SNPs in six key genes within the NER pathway (ERCCI, XPA, XPC, XPD, XPF, and XPG). The odds ratio (OR) and 95% confidence interval (CI) were calculated to measure the strength of associations. We identified significant associations between two XPD SNPs and Wilms tumor risk. The XPD rs3810366 polymorphism significantly enhanced Wilms tumor risk (dominant model: adjusted OR = 2.12, 95% CI = 1.26–3.57). Likewise, XPD rs238406 conferred a significantly increased risk for the disease (dominant model: adjusted OR = 2.30, 95% CI = 1.40–3.80; recessive model: adjusted OR = 1.64, 95% CI = 1.11–2.44). Moreover, online expression quantitative trait locus (eQTL) analysis demonstrated that these two polymorphisms significantly affected XPD gene expression in transformed fibroblast cells. Our study provides evidence of the association between the two XPD polymorphisms and Wilms tumor risk. However, these findings warrant validation in larger studies.

INTRODUCTION

Wilms tumor (WT) is a complex childhood embryonal tumor of the kidney, affecting about one child per 10,000 worldwide under 15 years of age. WT is derived from the embryonal nephric mesenchyme. It is characterized by the copresence of the whole spectrum of nephrogenic differentiation, from primitive blastema to mature epithelial and stromal elements, which normally appear in the different developmental stages of the kidney. Compared with other cancers, treatment of WT has been quite successful. Several clinical trials have achieved overall survival rates of over 90%, carried out by the Children’s Oncology Group (COG), the International Society of Pediatric Oncology (SIOP), and others.1 The encouraging outcomes of patients in clinical trials largely benefit from personalized therapy founded on clinical (e.g., age, tumor size, volume, and response to chemotherapy) and genetic (e.g., loss of heterozygosity [LOH]) at chromosomes 1p and 16q) risk factors. Despite the favorable prognosis of WT, it should be noted that approximately 25% survivors experience severe chronic disorders. Moreover, 25% WT patients have high-risk WT (i.e., poor histologic and molecular characteristics, tumors on both sides, and relapsed disease), and their survival rates are below 90%. Therefore, it is indispensable to refine treatment modalities to reduce sequelae and complications and to develop novel therapies for high-risk WT.

WT is a genetically heterogeneous and complex disease. Well established genetic risk factors include mutations in Wnt/β-catenin pathway-related Wilms tumor gene 1 (WT1), catenin beta 1 (CTNNB1), and Wilms Tumor gene on the X chromosome (WTX), which are involved in the etiology of approximately one-third of WT.2 Moreover, LOH of chromosome 16q, gain of chromosome 1q, and microRNA (miRNA)-processing gene mutations are also frequently observed in WT.3,4 However, the alterations of additional genes that contribute to Wilms tumorigenesis still warrant intensive investigations.

The human genome is frequently subjected to damage resulting from both environmental agents (e.g., UV light and inhaled cigarette smoke) and endogenous weak mutagens (reactive oxygen species and metabolites like alkylating agents). To maintain genome integrity, several DNA repair mechanisms continuously inspect chromosomes to fix damaged nucleotide residues induced by the great variety of DNA-damaging agents. These mechanisms include base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR), which are responsible for distinct forms of DNA damage.5,6 NER primarily eliminates bulky adducts arising from exposure to...
Table 1. Association of Polymorphisms in Nucleotide Excision Repair Pathway Genes with Wilms Tumor Susceptibility

| Gene    | SNP          | Allele | Case (n = 145) | Control (n = 531) | Adjusted OR (95% CI) | p' | Adjusted OR (95% CI) | p' | HWE |
|---------|--------------|--------|---------------|------------------|----------------------|----|----------------------|----|-----|
| ERCCI   | rs2298881    | A      | 213           | 87              | 0.89 (0.62–1.30)     | 0.557 | 0.85 (0.50–1.44)     | 0.544 | 0.072 |
| ERCCI   | rs3212986    | A      | 236           | 64              | 1.35 (0.93–1.98)     | 0.118 | 1.09 (0.63–1.98)     | 0.758 | 0.519 |
| ERCCI   | rs11615      | G      | 302           | 44              | 0.90 (0.62–1.31)     | 0.576 | 0.64 (0.29–1.39)     | 0.261 | 0.043 |
| XPA     | rs1800975    | T      | 124           | 126             | 1.14 (0.73–1.79)     | 0.566 | 1.31 (0.87–1.98)     | 0.203 | 0.178 |
| XPA     | rs3176752    | G      | 408           | 8               | 1.19 (0.78–1.82)     | 0.419 | 2.55 (0.81–8.00)     | 0.110 | 0.975 |
| XPC     | rs2228001    | A      | 218           | 68              | 1.26 (0.86–1.84)     | 0.238 | 1.06 (0.62–1.82)     | 0.827 | 0.948 |
| XPC     | rs2228000    | C      | 205           | 76              | 0.80 (0.55–1.16)     | 0.232 | 1.05 (0.63–1.76)     | 0.851 | 0.988 |
| XPC     | rs2607775    | G      | 477           | 0               | 0.71 (0.36–1.40)     | 0.328 |                    |     |     |
| XPC     | rs1870134    | G      | 339           | 26              | 1.04 (0.71–1.52)     | 0.862 | 0.27 (0.06–1.17)     | 0.080 | 0.335 |
| XPC     | rs2229090    | G      | 191           | 85              | 1.04 (0.70–1.53)     | 0.853 | 0.86 (0.51–1.46)     | 0.580 | 0.994 |
| XPD     | rs3810366    | C      | 128           | 155             | 2.12 (1.26–3.57)     | 0.005c | 1.26 (0.85–1.87)     | 0.242 | 0.143 |
| XPD     | rs238406     | G      | 149           | 132             | 2.30 (1.40–3.80)     | 0.001c | 1.64 (1.11–2.44)     | 0.014c | 0.186 |
| XPD     | rs313811     | T      | 462           | 4               | 0.87 (0.50–1.54)     | 0.639 | 0.86 (0.10–7.80)     | 0.895 | 0.312 |
| XPF     | rs2276466    | G      | 301           | 29              | 1.08 (0.74–1.57)     | 0.696 | 1.60 (0.79–3.24)     | 0.188 | 0.543 |
| XPG     | rs2094258    | C      | 203           | 74              | 0.81 (0.55–1.17)     | 0.260 | 0.94 (0.55–1.62)     | 0.819 | 0.701 |
| XPG     | rs751402     | T      | 208           | 82              | 1.20 (0.81–1.76)     | 0.366 | 0.93 (0.54–1.58)     | 0.776 | 0.380 |
| XPG     | rs2296147    | T      | 343           | 18              | 0.87 (0.59–1.29)     | 0.492 | 1.06 (0.39–2.92)     | 0.910 | 0.583 |
| XPG     | rs1047768    | T      | 307           | 26              | 1.19 (0.82–1.72)     | 0.371 | 1.20 (0.53–2.73)     | 0.659 | 0.409 |
| XPG     | rs873601     | G      | 137           | 124             | 0.88 (0.58–1.33)     | 0.547 | 1.04 (0.67–1.61)     | 0.859 | 0.686 |

HWE, Hardy-Weinberg equilibrium.  
*aAdjusted for age and gender for the dominant model.  
*bAdjusted for age and gender for the recessive model.  
*cThe results if the 95% CI excluded 1 or p < 0.05.

Environmental agents. Many core proteins are involved in NER, among which xeroderma pigmentosum A (XPA) to XPG were identified from xeroderma pigmentosum. Moreover, excision repair cross-complementation group 1 (ERCCI), replication protein A (RPA), RAD23 homolog A (RAD23A), and RAD23 homolog B (RAD23B) also participate in NER. SNPs in NER genes have been linked to various cancer types, including lung, bladder, skin, breast, prostate, and head and neck cancers. Accumulating evidence has indicated that some SNPs in DNA repair genes or their regulatory elements can induce phenotypical alterations, affecting DNA repair capacity and promoting cancer initiation and development. In this study, we genotyped 19 potential functional NER pathway gene SNPs in 145 WT cases and 531 controls to intensively investigate their association with WT risk.

RESULTS
Characteristics of the Study Population
The current study was composed of 145 cases and 531 cancer-free controls (average age: 26.17 ± 21.48 months versus 29.73 ± 24.86 months). No statistically significant differences in age (p = 0.725) and gender (p = 0.956) were detected between the case and control groups. Participants were stratified by following the National Wilms Tumor Study-5 (NWTS-5) criteria. Specifically, 4 (2.76%), 49 (33.79%), 50 (34.48%), and 33 (22.76%) individuals were determined to bear clinical stage I, II, III, and IV tumors, respectively. It should be noted that evaluation and staging failed in 9 cases (6.21%) because of inadequate information (Table S1).

Associations between NER Pathway Gene SNPs and WT Susceptibility
In total, 19 SNPs in the NER pathway genes were genotyped in 145 cases and 531 controls. Specifically, there were 3, 2, 5, 3, 1, and 5 SNPs in the ERCCI, XPA, XPC, XPD, XPF, and XPG genes, respectively (Table 1). Of them, two SNPs in the XPD gene were found to significantly modify WT risk (Figures 1 and 2). The XPD rs3810366 polymorphism was found to significantly increase the risk of developing WT (recessive model: adjusted odds ratio [OR] = 2.12, 95% confidence interval [CI] = 1.26–3.57), whereas XPD rs238406 was significantly associated with an increased risk of the disease (dominant model: adjusted OR = 2.30, 95% CI = 1.11–2.44).

Stratified Analysis
Participants were further stratified by age, gender, and clinical stage (Table 2). Stratified analyses were performed for the two significant
XPD polymorphisms (rs3810366 and rs238406) and the combined risk genotypes of the XPD gene. Intriguingly, the XPD rs3810366 polymorphism was shown to associate with WT risk in older participants (>18 months of age), males, and those with clinical stage I/II disease. Moreover, the association with the rs238406 polymorphism remained significant among all strata, except for females. A borderline significant association was found in females. We next evaluated the combined effects of XPD polymorphisms. Among the participants carrying 1–3 risk genotypes, males and older children (>18) were at significantly elevated risk of WT compared with non-carriers. Children with 1–3 risk genotypes were more likely to develop stage I/II disease.

Haplotype Analysis
The effects of the haplotypes of the XPD gene were also explored. We found that the GTG haplotype was significantly associated with an increased WT risk compared with the CCG reference haplotype in the order of rs3810366, rs238406, and rs13181 (Table 3).

Expression Quantitative Trait Loci
We further explored biological effects of the two significant SNPs in the XPD gene expression by investigating a public database, GTEx portal. We observed that genotypes of both SNPs were significantly associated with XPD gene expression in transformed fibroblasts cells (Figure 3).

DISCUSSION
Several lines of evidence implicate genetic variants in WT: ethnic differences in WT susceptibility are more prominent than geographic differences, WT occurs in both sporadic and familial forms, and several syndromes, harboring mutations in WT1 or epigenetic defects at 11p15.3, had a greatly increased risk of WT. A more comprehensive understanding of tumor biology would help us to make progress in prevention, therapy, and prognosis of this disease. A genome-wide association study (GWAS) has been performed in 757 cases and 1,879 controls, attempting to determine common WT-predisposing variants. Ten significant SNPs were further validated in two separate study populations from the United Kingdom (769 cases and 2,814 controls) and the United States (719 cases and 1,037 controls). Two loci showed significant association with WT susceptibility: 2p24 (rs3755132 and rs807624) and 11q14 (rs790356). In this study, we explore the association of NER pathway gene SNPs and WT risk in 145 neuroblastoma cases and 531 healthy controls. With the same study population, we validated that SNPs in several genes were associated with WT, including the BARD1,19 TP53,20 LIN28B,21 LOM1,22 and HACE123 genes. Overall, 19 potential functional SNPs in 6 key NER genes (ERCC1, XPA, XPC, XPD, XPF, and XPG) were genotyped. The association of DNA repair gene SNPs with cancer susceptibility has been widely investigated worldwide. A number of SNPs within the NER pathway have been found to associate with the risk of various types of cancer in Chinese populations, including laryngeal cancer,10 pancreatic cancer,11 breast cancer,13 prostate cancer,13 gastric cancer,14 colorectal cancer,24 and hepatocellular cancer.25 Among six key NER genes, association with significantly increased WT risk was identified for two SNPs (rs3810366 and rs238406) in the XPD gene. The XPD gene encodes a 760-amino acid polypeptide of 87 kDa that participates in transcription-coupled NER. Defects in this gene have been known to be related to three different conditions: the cancer-prone syndrome xeroderma pigmentosum complementation group D, photosensitive trichothiodystrophy, and Cockayne syndrome.26 XPD rs238406 (R156R) was found to be marginally significantly associated with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma.27 Romanowicz et al.15 and Michalska et al.28 identify this SNP as a risk factor for ovarian cancer and endometrial cancer, respectively, in Poland. In a Chinese population, rs238406 significantly increased esophageal squamous cell carcinoma susceptibility. However, studies of XPD rs3810366 (at promoter −114) are relatively few. Several studies showed no association between rs3810366 and cancer susceptibility in Taiwan.2,12,29,30
Numerous SNPs have been proven to be functional. Most recently, an uncommon missense polymorphism, rs149418249 (c.C1520T, p.P507L) located in the TPP1 (alias ACD, gene ID 65057), a component of the shelterin complex, was reported to confer colorectal cancer susceptibility. This variant can cause telomere dysfunction by disrupting TPP1 interaction with TIN2. Moreover, an exome-wide analysis identified a variant (rs138478634) in CSB that decreased expression of NER genes (e.g., ERCC1, XPB, XPG, and XPC) in vitro and functional analyses of SNPs are needed to validate our findings.

Several limitations should be noted in this study. First, we performed this association study in a relatively small number of samples. It cannot be ruled out that chance may account for one or more of the associations in the present study. Therefore, replication of our findings is encouraged. Second, WT carcinogenesis resulted from the 3' UTR of genes; a minor allele frequency of less than 5% in the Guangzhou Women and Children’s Medical Center.51–23,35 All tumors were histopathologically confirmed. Blood samples were collected at the time of diagnosis. Specimens were annotated with information including age at diagnosis, sex, and disease stage based on the NWTS-5 criteria. The 531 cancer-free controls were selected from children visiting the same hospital for a regular physical examination during the same period of time.36–39 Frequency matching was performed for cases and controls on age and sex. Exclusion criteria included other types of tumors, secondary or recurrent tumors, and previous chemotherapy or radiotherapy. Participants were limited to the ethnic Chinese Han population. Prior to sample collection, all participants or their guardians were required to sign written informed consent compliant with the Declaration of Helsinki. The study was authorized by the Institutional Review Board of Guangzhou Women and Children’s Medical Center.

SNP Selection and Genotyping
SNPs were retrieved from the dbSNP database (https://www.ncbi.nlm.nih.gov/projects/SNP). We finally included 19 potentially functional SNPs in the core genes in the NER pathway that fit the following selection criteria: location of candidate SNPs were limited to the 5' UTR, upstream promoter region, coding region, as well as the 3' UTR of genes; a minor allele frequency of less than 5% in Chinese Han populations; and lack of linkage disequilibrium (R^2 < 0.8) between each SNP pair. Potential functions of SNPs were predicted using SNPInfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html); candidate SNPs should be able to modify the function of transcription factor binding sites or microRNA binding sites. Eventually, the following polymorphisms were included: ERCC1 (rs2298881 C > A, rs11615 G > A, rs3212986 C > A), XPA (rs1800975 G > A, rs3176752 C > A), XPC

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**Figure 2. Forest Plot for the Association between NER Gene Polymorphisms and Wilms Tumor Susceptibility under the Recessive Model (BB versus AA/AB)**

For each SNP, the estimates of odds ratio and its 95% confidence interval are plotted with a box and a horizontal line.
DNA was collected from peripheral blood samples of participants with the QIAamp DNA Blood Mini Kit (QIAGEN, Valencia, CA). We carried out genotyping on the platform of the TaqMan real-time PCR method on a 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). The technique details were described previously.40–42 Quality control was strictly executed; four duplicate positive controls and four negative controls (omitting DNA template) were loaded, along with samples in each of the 384-well plates. Furthermore, 10% of the tested samples were randomly picked and genotyped for a second time.43–46 We observed an overall genotype concordance rate of 100% for each SNP in the subsequent genotyping.

**Genotype-Phenotype Association**

eQTL are regions of the genome containing DNA sequence variants that influence the expression level of one or more genes. We further explored the effects of the two significant SNPs on XPD gene expression by investigating a public database, GTEx portal (https://www.gtexportal.org/). The data in transformed fibroblasts were described previously.47

**Statistics**
The Hardy-Weinberg equilibrium (HWE) was determined by using the goodness-of-fit χ² test in control subjects. Student’s t test was used to compare the differences in age between cases and controls. χ² tests were used to evaluate differences in the categorical variables between cases and controls, including sex and distributions of allele frequencies. Multivariate logistic regression analysis was performed. ORs and 95% CIs were computed to determine the strength of the association between SNPs and WT risk. We further carried out

### Table 2. Stratification Analysis of XPD Gene Variant Genotypes with Wilms Tumor Risk

| Variables | rs3810366 (Case/Control) | rs238406 (Case/Control) | Risk Genotype (Case/Control) |
|-----------|--------------------------|-------------------------|-----------------------------|
| Age (Months) | AOR (95% CI) | AOR (95% CI) | AOR (95% CI)  |
| ≤18 | 10/56 | 56/177 | 1.74 (0.83–3.64) | 0.142 | 10/65 | 56/168 | 2.15 (1.03–4.46) | 0.041 |
| >18 | 9/72 | 70/226 | 2.48 (1.18–5.21) | 0.017 | 11/84 | 68/214 | 2.43 (1.23–4.83) | 0.011 |
| Gender | | | | | | | | |
| Females | 10/59 | 54/174 | 1.85 (0.89–3.87) | 0.102 | 11/67 | 53/166 | 1.95 (0.96–3.96) | 0.066 |
| Males | 9/69 | 72/229 | 2.38 (1.13–5.02) | 0.022 | 10/82 | 71/216 | 2.69 (1.32–5.47) | 0.006 |
| Clinical Stages | | | | | | | | |
| I/II | 6/128 | 47/403 | 2.56 (1.06–6.15) | 0.036 | 7/149 | 46/382 | 2.58 (1.13–5.86) | 0.024 |
| III/IV | 12/128 | 71/403 | 1.87 (0.98–3.56) | 0.057 | 13/149 | 70/382 | 2.09 (1.12–3.90) | 0.020 |

AOR, adjusted odds ratio.  
aObtained in logistic regression models with adjustment for age and gender.  
bThe results if the 95% CI excluded 1 or p < 0.05.

### Table 3. The Frequency of Inferred Haplotypes of the XPD Gene and Wilms Tumor Risk

| Haplotypes | Cases (n = 290) | Controls (n = 1,062) | OR (95% CI) | p | AOR (95% CI)  | p  |
|-----------|----------------|---------------------|-------------|---|--------------|---|
| CGG       | 10 (3.45) | 48 (4.52) | 1.00 | – | 1.00 | – |
| CGT       | 120 (41.48) | 456 (42.94) | 1.05 (0.52–2.15) | 0.888 | 1.08 (0.53–2.21) | 0.658 |
| CTG       | 0 (0.00) | 0 (0.00) | – | – | – | – |
| CTT       | 4 (1.38) | 0 (0.00) | – | – | – | – |
| GGG       | 2 (0.69) | 20 (1.88) | 0.48 (0.10–2.39) | 0.370 | 0.47 (0.09–2.34) | 0.355 |
| GGT       | 3 (1.03) | 24 (2.26) | 0.60 (0.15–2.39) | 0.468 | 0.63 (0.16–2.49) | 0.505 |
| GTG       | 5 (1.70) | 5 (0.47) | 5.76 (1.47–22.63) | 0.012 | 6.10 (1.54–24.09) | 0.010 |
| GTT       | 165 (56.90) | 509 (47.93) | 1.56 (0.77–3.15) | 0.218 | 1.59 (0.79–3.21) | 0.198 |

aThe haplotype order was rs3810366, rs238406, and rs13181.  
bObtained in logistic regression models with adjustment for age and gender.  
cThe results if the 95% CI excluded 1 or p < 0.05.
multivariate analysis using an unconditional logistic regression model to calculate ORs, with adjustment for age and sex. All statistical analyses were accomplished using version 9.1 SAS software (SAS Institute, Cary, NC). Two-sided p < 0.05 was adopted as a criterion of significance.

SUPPLEMENTAL INFORMATION
Supplemental Information includes one table and can be found with this article online at https://doi.org/10.1016/j.omtn.2018.08.002.

AUTHOR CONTRIBUTIONS
J.Z., W.F., J.H., and G.-C.L. designed and performed the study and wrote the manuscript. W.F., W.J., and H.X. collected the samples and information. J.Z. and J.H. participated in data analysis. W.F., W.J., and H.X. coordinated the entire study. All authors reviewed the final manuscript.

CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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REFERENCES
1. Dome, J.S., Graf, N., Geller, J.L., Fernandez, C.V., Muller, E.A., Spreafico, F., Van den Heuvel-Eibrink, M., and Pritchard-Jones, K. (2015). Advances in Wilms Tumor Treatment and Biology: Progress Through International Collaboration. J. Clin. Oncol. 33, 2999–3007.
2. Dome, J.S., and Huff, V. (1993). Wilms Tumor Predisposition. In GeneReviews, R.A. Pagon, et al., eds. (University of Washington).
3. Rivera, M.N., and Haber, D.A. (2005). Wilms' tumor: connecting tumorigenesis and organ development in the kidney. Nat. Cancer Inst. 5, 699–712.
4. Gadd, S., Huff, V., Walt, A.L., Ooms, A.H.A.G., Armstrong, A.E., Gerhard, D.S., Smith, M.A., Auivil, J.M.G., Meerzaman, D., Chen, Q.R., et al. (2017). A Children's Oncology Group and TARGET initiative exploring the genetic landscape of Wilms tumor. Nat. Genet. 49, 1487–1494.
5. Wood, R.D., Mitchell, M., Sgouros, J., and Lindahl, T. (2001). Human DNA repair genes. Science 291, 1284–1289.
6. Sancar, A. (1995). DNA repair in humans. Annu. Rev. Genet. 29, 69–105.
7. Kamler, I., Karakasilioti, I., and Garinis, G.A. (2012). Nucleotide excision repair: new tricks with old bricks. Trends Genet. 28, 566–573.
8. Cheng, L., Sturgis, E.M., Eicher, S.A., Spitz, M.R., and Wei, Q. (2002). Expression of nucleotide excision repair genes and the risk for squamous cell carcinoma of the head and neck. Cancer 94, 393–397.
9. Ji, H.X., Chang, W.S., Tsai, C.W., Wang, J.Y., Huang, N.K., Lee, A.S., Shen, M.Y., Chen, W.Y., Chiang, Y.C., Shih, T.C., et al. (2015). Contribution of DNA Repair Xeroderma Pigmentosum Group D Genotype to Gastric Cancer Risk in Taiwan. Anticancer Res. 35, 4975–4981.
10. Sun, Y., Tan, L., Li, H., Qin, X., and Liu, J. (2015). Association of NER pathway gene polymorphisms with susceptibility to laryngeal cancer in a Chinese population. Int. J. Clin. Exp. Pathol. 8, 11615–11621.
11. Zhao, F., Shang, Y., Zeng, C., Gao, D., and Li, K. (2015). Association of single nucleotide polymorphisms of DNA repair genes in NER pathway and susceptibility to pancreatic cancer. Int. J. Clin. Exp. Pathol. 8, 11579–11586.
12. Chang, W.S., Yueh, T.C., Tsai, C.W., Ji, H.X., Wu, C.N., Wang, S.C., Lai, Y.L., Hsu, S.W., Hsieh, M.H., Hsiao, C.L., et al. (2016). Contribution of DNA Repair Xeroderma Pigmentosum Group D Genotypes to Colorectal Cancer Risk in Taiwan. Anticancer Res. 36, 1657–1663.
13. He, B.S., Xu, T., Pan, Y.Q., Wang, J.J., Cho, W.C., Lin, K., Sun, H.L., Gao, T.Y., and Wang, S.K. (2016). Nucleotide excision repair pathway gene polymorphisms are linked to breast cancer risk in a Chinese population. Oncotarget 7, 84872–84882.
14. Liu, J., Sun, L., Xu, Q., Tu, H., He, C., Xing, C., and Yuan, Y. (2016). Association of nucleotide excision repair pathway gene polymorphisms with gastric cancer and atrophic gastritis risks. Oncotarget 7, 6972–6983.
15. Romanowicz, H., Michalska, M.M., Samulak, D., Malinowski, J., Szaflik, T., Bienkowski, J., and Smolarz, B. (2017). Association of R156R single nucleotide polymorphism of the ERCC2 gene with the susceptibility to ovarian cancer. Eur. J. Obstet. Gynecol. Reprod. Biol. 208, 36–40.
16. Wang, M., Li, Q., Gu, C., Zhu, Y., Yang, Y., Wang, J., Jin, L., He, J., Ye, D., and Wei, Q. (2017). Polymorphisms in nucleotide excision repair genes and risk of primary prostate cancer in Chinese Han populations. Oncotarget 8, 24362–24371.
17. Beckwith, J.B. (1998). National Wilms Tumor Study: an update for pathologists. Pediatr. Dev. Pathol. 1, 79–84.
18. Turnbull, C., Perdeux, E.R., Pernet, D., Naranjo, A., Renwick, A., Seal, S., Manoel-Xicola, R.M., Hanks, S., Slade, I., Zachariou, A., et al. (2012). A genome-wide association study identifies susceptibility loci for Wilms tumor. Nat. Genet. 44, 681–684.
19. Fu, W., Zhu, J., Xiong, S.W., Jia, W., Zhao, Z., Zhu, S.B., Hu, J.H., Wang, F.H., Xia, H., He, J., and Liu, G.C. (2017). BARD1 Gene Polymorphisms Confer Nephroblastoma Susceptibility. EBioMedicine 16, 101–105.

20. Fu, W., Zhuo, Z.J., Jia, W., Zhu, J., Zhuo, S.B., Lin, Z.F., Wang, F.H., Xia, H., He, J., and Liu, G.C. (2017). Association between TP53 gene Arg72Pro polymorphism and Wilms’ tumor risk in a Chinese population. Oncotarget 8, 1149–1154.

21. Fu, W., Liu, G.C., Zhao, Z., Jia, W., Zhu, S.B., Hu, J.H., Wang, F.H., He, J., and Xia, H. (2018). The correlation between LIN28B gene potentially functional variants and Wilms tumor susceptibility in Chinese children. J. Clin. Lab. Anal. 32, e22200.

22. Liu, G.C., Zhuo, Z.J., Zhu, J., Liu, W., Zhao, Z., Hu, J.H., He, J., Wang, F.H., and Fu, W. (2017). Associations between LMO1 gene polymorphisms and Wilms’ tumor susceptibility. Oncotarget 8, 50665–50672.

23. Jia, W., Deng, Z., Zhu, J., Fu, W., Zhu, S., Zhang, L.Y., Hu, J., Wang, F., Xia, H., Liu, G.C., and He, J. (2017). Association Between HACE1 Gene Polymorphisms and Wilms’ Tumor Risk in a Chinese Population. Cancer Invest. 35, 633–638.

24. Hua, R.X., Zhuo, Z.J., Zhu, J., Zhang, S.D., Xue, W.Q., Zhang, J.B., Xu, H.M., Li, X.Z., Zhang, P.F., He, J., and Jia, W.H. (2016). XPG Gene Polymorphisms Contribute to Colorectal Cancer Susceptibility: A Two-Stage Case-Control Study. J. Cancer 7, 1731–1739.

25. Wang, B., Xu, Q., Yang, H.W., Sun, L.P., and Yuan, Y. (2016). The association of six polymorphisms of five genes involved in three steps of nucleotide excision repair pathways with hepatocellular cancer risk. Oncotarget 7, 20357–20367.

26. Andressoo, J.O., Mitchell, J.R., de Wit, J., Hoogstraten, D., Volker, M., Toussaint, W., Speksnijder, E., Beems, R.B., van Steeg, H., Jans, J., et al. (2006). An Xpd mouse model for the combined xeroderma pigmentosum/Cockayne syndrome exhibiting both cancer predisposition and segmental progeria. Cancer Cell 10, 121–132.

27. Han, L., Lee, C.K., Pang, H., Chan, H.T., Lo, L.L., Lam, S.K., Cheong, T.H., and Ho, J.C. (2017). Genetic predisposition to lung adenocarcinoma among never-smoking Chinese with different epidermal growth factor receptor mutation status. Lung Cancer 114, 79–89.

28. Michalska, M.M., Samulak, D., Jabłoński, F., Romanowicz, H., and Smolars, B. (2016). The R156R ERCC2 polymorphism as a risk factor of endometrial cancer. Tumour Biol. 37, 2171–2176.

29. Chang, C.H., Wang, R.F., Tsai, R.Y., Wu, H.C., Wang, C.H., Tsai, C.W., Chang, C.L., Tsou, Y.A., Liu, C.S., and Bau, D.T. (2009). Significant association of XPD codon 312 single nucleotide polymorphism with bladder cancer susceptibility in Taiwan. Anticancer Res. 29, 3903–3907.

30. Wang, H.C., Liu, C.S., Wang, C.H., Tsai, R.Y., Tsai, C.W., Wang, R.F., Chang, C.H., Chen, Y.S., Chiu, C.F., Bau, D.T., and Huang, C.Y. (2010). Significant association of XPD Asp312Asn polymorphism with breast cancer in Taiwanese patients. Chin. J. Physiol. 53, 130–135.

31. Li, J., Chang, J., Tian, J., Ke, J., Zhu, Y., Yang, G., Gong, Y., Zou, D., Deng, X., Yang, N., et al. (2018). A rare variant F507L in TPPI interrupts TPPI-TIN2 interaction, influences telomere length, and confers colorectal cancer risk in Chinese population. Cancer Epidemiol. Biomarkers Prev. Published online June 11, 2018. https://doi.org/10.1158/1055-9965.EPI-18-0099.

32. Chang, J., Zhong, R., Tan, J., Li, J., Zhai, K., Ke, J., Lou, J., Chen, W., Zhu, B., Shen, N., et al. (2018). Exome-wide analyses identify low-frequency variant in CYP26B1 and additional coding variants associated with esophageal squamous cell carcinoma. Nat. Genet. 50, 338–343.

33. Xiao, S., Cui, S., Lu, X., Guan, Y., Li, D., Liu, Q., Cai, Y., Jin, C., Yang, J., Wu, S., and van der Straaten, T. (2016). The ERCC2/XPD Lys751Gln polymorphism affects DNA repair of benzo[a]pyrene induced damage, tested in an in vitro model. Toxicol. In Vitro 34, 300–308.

34. Han, P., Gao, F., Liu, H., Liu, Z., Shi, Q., Troy, J.D., Owzar, K., Lee, W., Zevallos, J.P., Sturgis, E.M., and Wei, Q. (2017). Reduced mRNA expression of nucleotide excision repair genes in lymphocytes and risk of squamous cell carcinoma of the head and neck. Carcinogenesis 38, 504–510.

35. Zhu, J., Jia, W., Wu, C., Fu, W., Xia, H., Liu, G., and He, J. (2018). Base Excision Repair Gene Polymorphisms and Wilms Tumor Susceptibility. EBioMedicine 33, 88–93.

36. He, J., Wang, F., Zhu, J., Zhang, Z., Zou, Y., Zhang, R., Yang, T., and Xia, H. (2017). The TP53 gene rs1042522 C>G polymorphism and neuroblastoma risk in Chinese children. Aging (Albany N.Y.) 9, 852–859.

37. He, J., Zou, Y., Wang, T., Zhang, R., Yang, T., Zhu, J., Wang, F., and Xia, H. (2017). Genetic Variations of GWAS-Identified Genes and Neuroblastoma Susceptibility: a Replication Study in Southern Chinese Children. Transl. Oncol. 10, 936–941.

38. He, J., Zou, Y., Liu, X., Zhu, J., Zhang, J., Zhang, R., Yang, T., and Xia, H. (2018). Association of Common Genetic Variants in Pre-microRNAs and Neuroblastoma Susceptibility: A Two-Center Study in Chinese Children. Mol. Ther. Nucleic Acids 11, 1–8.

39. He, J., Wang, F., Zhu, J., Zhang, R., Yang, T., Zou, Y., and Xia, H. (2016). Association of potentially functional variants in the XPG gene with neuroblastoma risk in a Chinese population. J. Cell. Mol. Med. 20, 1481–1490.

40. Zhu, J., Wang, M., He, J., Jia, M., Wang, J.C., Jin, L., Wang, X.F., Yang, Y.J., Xiang, J.Q., and Wei, Q. (2016). Polymorphisms in the AKT1 and AKT2 genes and esophageal squamous cell carcinoma risk in an Eastern Chinese population. J. Cell. Mol. Med. 20, 666–677.

41. Zhu, J., Wang, M., Zhu, M., He, J., Wang, J.C., Jin, L., Wang, X.F., Xiang, J.Q., and Wei, Q. (2015). Associations of PIK3R1 and mTOR polymorphisms with esophageal squamous cell carcinoma risk and gene-environment interactions in Eastern Chinese populations. Sci. Rep. 5, 8250.

42. Hua, R.X., Zhuo, Z.J., Zhu, J., Jiang, D.H., Xue, W.Q., Zhang, S.D., Zhang, J.B., Li, X.Z., Zhang, P.F., Jia, W.H., et al. (2016). Association between genetic variants in the XPG gene and gastric cancer risk in a Southern Chinese population. Aging (Albany N.Y.) 8, 3311–3320.

43. Li, J., Zou, L., Zhou, Y., Li, L., Zhu, Y., Yang, G., Gong, Y., Lou, J., Ke, J., Zhang, Y., et al. (2017). A low-frequency variant in SMAD7 modulates TGF-β signaling and confers risk for colorectal cancer in Chinese population. Mol. Carcinog. 56, 1798–1807.

44. Lou, J., Gong, J., Ke, J., Tian, J., Zhang, Y., Li, Yang, Y., Zhuo, Y., Gong, Y., Li, L., et al. (2017). A functional polymorphism located at transcription factor binding sites, rs6095837 near LAMC1 gene, confers risk of colorectal cancer in Chinese populations. Carcinogenesis 38, 177–183.

45. Gong, J., Tian, J., Lou, J., Wang, X., Ke, J., Li, L., Yang, Y., Gong, Y., Zou, D., et al. (2018). A polymorphic MYC response element in KRTBD11 influences colorectal cancer risk, especially in interaction with an MYC-regulated SNP rs6983267. Ann. Oncol. 29, 632–639.

46. Zou, D., Lou, J., Ke, J., Mei, S., Li, J., Gong, Y., Yang, Y., Zou, Y., Tian, J., Chang, J., et al. (2018). Integrative expression quantitative trait locus-based analysis of colorectal cancer identified a functional polymorphism regulating SLCC2A5 expression. Eur. J. Cancer 93, 1–9.

47. Zhuo, Z.J., Liu, W., Zhang, J., Zhu, J., Zhang, R., Tang, J., Yang, T., Zou, Y., He, J., and Xia, H. (2018). Functional Polymorphisms at ERCC1/XPF Genes Confer Neuroblastoma Risk in Chinese Children. EBioMedicine 30, 113–119.