Research Paper

Base Excision Repair Gene Polymorphisms and Wilms Tumor Susceptibility

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A B S T R A C T

Base excision repair (BER) is the main mechanism to repair endogenous DNA lesions caused by reactive oxygen species. BER deficiency is linked with cancer susceptibility and premature aging. Single nucleotide polymorphisms (SNPs) within BER genes have been implicated in various human malignancies. Nevertheless, a comprehensive investigation of their association with Wilms tumor susceptibility is lacking. In this study, 145 cases and 531 sex and age-matched healthy controls were recruited. We systematically genotyped 18 potentially functional SNPs in six core BER pathway genes, using a candidate SNP approach. Logistic regression was employed to evaluate odds ratio (OR) and 95% confidence interval (CI) adjusted for age and gender. Several SNPs showed protective effects against Wilms tumors. Significant associations with Wilms tumor susceptibility were shown for hOGG1 rs1052133 (dominant: adjusted OR = 0.66, 95% CI = 0.45–0.96, \(P = 0.03\)), FEN1 rs1745138 (dominant: adjusted OR = 0.66, 95% CI = 0.45–0.95, \(P = 0.027\); recessive: adjusted OR = 0.54, 95% CI = 0.32–0.93, \(P = 0.027\)), and FEN1 rs4246215 (dominant: adjusted OR = 0.55, 95% CI = 0.38–0.80, \(P = 0.02\) ) polymorphisms. Stratified analysis was performed by age, gender, and clinical stage. Moreover, there was evidence of functional implication of these significant SNPs suggested by online expression quantitative trait locus (eQTL) analysis. Our findings indicate that common SNPs in BER genes modify susceptibility to Wilms tumor.

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1. Introduction

Wilms tumor is one of the most common pediatric cancers, approximately affecting 7–10 children per million under the age of 15 years in Western countries [5]. Its incidence rate (3.3 per million) is only half as great as in China [2]. Wilms tumor, featured by developing nephrogenic mesechyma, arises from pluripotent embryonic kidney precursor cells [4,38]. Although the disease was considered lethal decades ago, 85% cases can be cured with multi-modality therapy nowadays [10,24]. However, it is noteworthy that high risk patients (nearly 25%) still have relatively poor outcomes, including those with adverse histology and molecular signatures, bilateral disease, and relapse. Moreover, around 25% survivors encounter serious chronic health conditions [10]. One of critical factors in improving patient prognosis is to better understand genetic basis of this disease. Most Wilms tumors are sporadic. Until recently, comprehension of Wilms tumor genetics were restricted mainly to aberrant alterations in a number of genes including Wilms’ tumor protein 1 (WT1), β-catenin, tumor protein 53 (TP53), and the AMER1, as well as abnormality of 11p15 methylation [15,28,38]. Although recent genomic analyses of Wilms tumor revealed many previously unknown mutations in a variety of genes [16,34,42,45], there remain numerous essential knowledge gaps to fill regarding Wilms tumor susceptibility.

Cellular genome continuously undergoes both exogenous and endogenous DNA damage. The former DNA lesions result from environmental agents such as chemicals, ionizing radiation, and ultraviolet light. Alternatively, genome integrity can be also threatened endogenously by hydrolytic reactions and metabolic by-products. Reactive oxygen species is the primary metabolites that lead to most oxidant- or alklylation-induced base lesions [46]. If not repaired properly, these
lesions can cause defects in transcription or replication, mutations, and genomic instability. The base excision repair (BER) system is designated to eradicate most of endogenous DNA damage so as to maintain DNA stability. Impaired base repair ability has been linked to cancer and aging [29]. Numerous studies have demonstrated that single nucleotide polymorphisms (SNPs) in some key BER genes are associated with the risk of a wide spectrum of human malignancies [22]. Functional analysis indicated that BER activities were reduced in blood leukocytes of cancer patients [31, 43]. Polymorphisms in key BER genes may modify BER kinetics and capacity, which further alter cellular DNA repair ability and cause cell dysfunction, mutagenesis, and ultimately carcinogenesis [40, 43]. Thus far, no evidence of linkage between BER SNPs and Wilms tumor has been reported; however, a few studies suggest the implication of DNA repair genes in Wilms tumors [28, 30]. Due to their universal implications in carcinogenesis, we systematically investigated the association between SNPs within the BER pathway and Wilms tumor risk. We analyzed 18 potentially functional SNPs in 145 cases and 531 controls from the following core BER genes: poly ADP-ribose polymerase 1 (PARP1), human 8-oxoguanine DNA glycosylase (hOGG1), Flap endonuclease 1 (FEN1), apurinic endonuclease 1 (APEX1), ligase III (LIG3), and x-ray repair cross-complementing group 1 (XRCC1). Expression quantitative trait locus (eQTL) analysis was performed for significant SNPs.

2. Materials and Methods

2.1. Study Population

This study comprised 145 Wilms tumor cases and 531 cancer-free controls, who were frequency-matched to case subjects on age and gender (Supplemental Table 1). All patients were diagnosed with Wilms tumor in the Guangzhou Women and Children’s Medical Center. All participants recruited were Chinese Han children. Each participant or his/her guardian signed written informed consent in agreement with the Declaration of Helsinki. Details were elaborated in the previous publications [12–14, 21, 26]. An official approval of this study was endowed by the Institutional Review Board of Guangzhou Women and Children’s Medical Center.

2.2. SNP Selection and Genotyping

SNPs were picked from dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP), based on a number of criteria, involving SNP location in gene region, minor allele frequency, and linkage disequilibrium (LD) [52, 53]. LD is defined as associations among adjacent alleles, indicating ‘haplotypes’ inherited from single, familial chromosomes. LD between two SNPs are determined using the classical statistic $D'$, with $|D'|$ of 1 representing complete LD and no LD, respectively [35]. Human Haplotype Map project was launched to measure LD and common haplotype patterns because of their association with diseases. Haplovie is able to produce several pairwise measures of LD [3]. Given the inheritance pattern of SNPs in LD, only SNPs not in significant LD $(R^2 < 0.8)$ with each were chosen in the present study.

Selected SNPs were uploaded to SNPinfo (http://snpinfo.niehs.nih.gov/snpfunc.htm) website to further screen for potential functional candidates; SNPs were chosen only if they could influence the binding activities of transcription factor binding sites or microRNA binding sites as well as splicing. We ultimately included 18 potentially functional SNPs (Supplemental Table 2) within BER pathway: PARP1 (rs1136410, rs2666428, rs8679), hOGG1 (rs1052133, rs159153, rs293795), FEN1 (rs174538, rs4246215), APEX1 (rs1130409, rs1760944, rs3136817), LIG3 (rs1052536, rs3744356, rs4796030), and XRCC1 (rs1799782, rs25487, rs25485, rs915927).

Participants’ peripheral blood samples were lysed to isolate genomic DNA, utilizing QIAamp DNA Blood mini kit (QIAGEN Inc., Valencia, CA). Genotyping assays were run on 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). Taqman real-time PCR was performed and allele-specific probes labeled with fluorochrome VIC or FAM were used to differentiate wild-type and variant alleles [17, 27, 55]. An exhaustive description of methods could be found in previous publications [52, 53]. To ensure the quality of genotyping, duplicate positive and four negative controls was used in company with samples in each of 384-well plates. Additionally, 10% of the DNA specimens were randomly chosen and genotyped again. A genotype concordance rate of 100% was seen across the assays.

2.3. Expression Quantitative Trait Loci Analysis

eQTLs are referred to as genomic sites harboring DNA sequence variants that affect gene transcript levels. Genotype-Tissue Expression (GTEx) portal (https://www.gtexportal.org/) is an online tool analyzing the influence of SNPs on the expression levels of local or distant genes across normal tissues and transformed fibroblasts [54]. We utilized this tool to explore the impacts of significant SNPs on gene expression in the transformed fibroblasts. The GTEx project aimed to develop a public database that can facilitate the scientific community to study the association between genetic variation and gene expression in human tissues. Details on aim, design, workflow, and statistical methods development and data analysis of this project can be found in a previous publication [8].

2.4. Statistics

Departure from Hardy–Weinberg equilibrium (HWE) for all SNPs was tested in this genetic association study, with the utilization of the goodness-of-fit chi-square test. Unconditional logistic regression analysis was applied to determined odds ratios (ORs) and 95% confidence intervals (CIs) associating the polymorphisms with the risk of Wilms tumor; the associations were further adjusted for age and gender using multivariate logistic regression analysis. The distributions of allele frequencies of SNPs and gender were compared between all patients and controls using two-sided chi-square test. The Student t-test was used for continuous variables. The website tool SNAP v2.2 (http://www.broadinstitute.org/mpg/snap/index.php) was employed to examine LD between each pair of SNPs. A version 9.1 TAS software (SAS Institute, Cary, NC) was used to complete all statistical analyses [18, 19]. A two-sided P value < .05 was regarded as a criterion of significance.

3. Result

3.1. Study Population

The characteristics of the study population were listed in the Supplemental Table 1, which have been exhaustively presented in previously publications [12–14, 21, 26]. Briefly, this study population consisted of 145 cases and 531 sex and age-matched healthy controls. Cases and controls aged under 15 years old, ranging from 1 to 132 and 0.07–156 months, respectively. There was no significant difference in the average age between cases and control. Gender distributed equivalently between two groups. Tumor staging was performed in conformity with the NWTS-5 criteria.

3.2. Association Study between the NER SNPs and Wilms Tumor Risk

The observed genotype distributions for all SNPs were consistent with HWE in controls, with an exception of APEX1 rs1130409 $(P = .019)$. In the single locus analysis, three BER gene SNPs have been shown to modestly modify Wilms tumor susceptibility, while no effect was observed for the rest of SNPs under dominant and recessive models (Table 1). First of all, we found that carriers of hOGG1 rs1052133 variant alleles showed decreased susceptibility to Wilms tumor at an adjusted OR of 0.66 (dominant: 95% CI = 0.45–0.96, P = .030). Second, FEN1 rs174538 variant alleles was shown to negatively associate with
The results were in bold, if the 95% CI excluded 1 or the \( FEN1 \) gene also had potential protective effect on Wilms tumor (dominant: adjusted OR = 0.55, 95% CI = 0.38–0.80). Table 2 showed potential protective effect on both early- and late-stage Wilms tumor.

3.3. Stratified Analysis

We next performed stratified analysis for significant SNPs by age, gender, and clinical stages (Table 2). The protective effect of the \( FEN1 \) rs4246215 remains prominent in both groups defined by age (≤18 and >18 months). Regarding gender, the protective association between the \( FEN1 \) rs4246215 and Wilms tumor susceptibility was detected in both females and males. The protective effect of \( hOGG1 \) rs1052133 polymorphism was pronounced in the subgroups with stage I/II disease, while the \( FEN1 \) rs4246215 showed potential protective effect on both early- and late-stage Wilms tumor.

3.4. Genotype-Phenotype Correlation

We further explored effects of allele-specific expression for the three significant SNPs by digging GTEx portal databases. None of genotypes of these SNPs was significantly associated with the expression levels of their host genes in the transformed fibroblasts. Intriguingly, these SNPs appear to influence expression of distant genes. The \( hOGG1 \) rs1052133 was associated with \( TTLL3 \) gene transcript levels. Both of the \( FEN1 \) SNPs (rs174538 and rs4246215) were correlated with the expression levels of \( FADA2 \) and \( TMEM258 \) genes.
4. Discussion

Genetic aberrations play an important role in Wilms tumor. For decades, only a few of genetic and epigenetic abnormalities were established in Wilms tumor as mentioned earlier. With the dramatic progresses in omics technologies, numerous causal genetic alterations in Wilms tumor have been discovered. For instance, several comprehensive genomic studies discovered mutations in miRNA processing genes (DROSHA, DGCRRB, and Dicer1) and genes related to kidney development (Six1 and Six2, and MYCN) [34, 42, 45]. Lately, a study of Wilms tumor genetic panorama determined recurrent mutations in a number of genes (Bcor, BcrLI, NONO, MAX, COL6A3, ASXL1, Map3K4, and ARID1A) [16]. Moreover, a genome-wide association study also identified a number of Wilms tumor susceptibility loci, including rs3755132 and rs807624 at 2p24, as well as rs790356 at 11q14. [44]

Some evidence suggests the roles of DNA repair genes in Wilms tumor. Folate pathway participates in DNA synthesis, methylation, and repair. Prenatal intake of folic acid is associated with a decrease in the risk of childhood malignancies including neuroblastoma and nephroblastoma [30]. A G80A (rs1051286) polymorphism in the RFC1 gene, encoding a folate transporter in the cell membrane, was found to associate with increased susceptibility to nephroblastoma and neuroblastoma in Brazilian children [30]. Mischietto et al., demonstrated that Wilms tumor with diffuse anaplasia harboring TP53 mutations were at significantly increased risk of recurrence in comparison of tumor without TP53 mutation [28]. This subgroup of tumors had increased genome instability and showed aberrant activity of genes related cell cycle and DNA repair [28]. A number of cancer susceptibility loci in the BER genes have been well documented [22]. However, no study concerning BER SNPs and Wilms tumor has been reported. In the current study, 18 potential functional SNPs in six BER genes were analyzed. Location-related potential functions of the studied SNPs were listed in the Supplemental Table 2. The function of a SNP is closely related to its specific position in gene region, including the untranslated region (UTR), coding sequence (CDS) or regulatory regions (i.e., promoter and enhancer). For instance, a nonsynonymous SNP in CDS may alter the amino acid sequence of a protein, whereas SNPs in microRNA response elements of 3′ UTR may disrupt or enhance the binding affinity of corresponding miRNAs, thereby causing aberrant expression of affected genes [41]. Overall, we observed that hOGG1 rs1052133, FEN1 rs174538, and rs4246215 polymorphisms were significantly associated with decreased susceptibility to Wilms tumor. Stratified analysis indicated that the associations were modified by age, gender, and clinical stages, to some extent. Some SNPs lost statistical significance in the stratified analysis, which could be a result of further reduced sample size in each analysis.

BER is the main mechanism to restore DNA lesions caused by oxidation, alkylation, and spontaneous decay [43]. BER deficiency contributes to cancer susceptibility and premature aging [29]. Based on functions, BER systems were categorized into a ‘short-patch’ BER pathway and a ‘long-patch’ pathway, which repairs one nucleotide and fills gaps of several nucleotides, respectively. Several key enzymes are required for base excision repair: 1) glycosylases recognizing and eliminating the damaged base, consequently generating an intact apurinic and aapyrimidinic sites, 2) AP-endonuclease 1 producing 3′-hydroxyl and 5′-deoxyribosephosphate ends, 3) polymerase beta’s removing the 5′-deoxyribosephosphate and introducing a new nucleotide to the notch, and 4) the scaffolding protein XRCC1 facilitating Lig3 to fill the gap [46, 48]. More enzymes are in engaged, while long-patch BER is initiated by repair bunched oxidative lesions, involving DNA pols α and/or ε, FEN1, PCNA and DNA ligase I [23]. Oxidative damages often change the nucleobase structure and its base-pairing attributes, thereby resulting in transition or transversion mutations [46]. A majority of human disease causing mutations arise from oxidative DNA damages [46]. Contributions of SNPs in the hOGG1 and FEN1 genes to cancer susceptibility have been intensively reviewed [20, 32, 50].

A recent meta-analysis investigated the influence of several BER polymorphisms on breast cancer risk [33]. Authors found that hOGG1 rs1052133 had potential protective effects on breast cancer in both Mongoloid and Caucasian populations [33]. A group carried out a meta-analysis for 22 polymorphisms in 17 DNA repair genes and colorectal cancer risk [1]. They observed no significant association between the hOGG1 rs1052133 and colorectal cancer risk (13 studies, 9682 cases and 12,938 controls). Further stratified analysis by tumor location indicated a significant association between the hOGG1 rs1052133 and rectal cancer risk [1]. In term of prostate cancer, significant affects of the hOGG1 rs1052133 were observed in the Asian and Caucasian populations [7]. In contrast, null association between the hOGG1 rs1052133 and gastric cancer risk was reported in a meta-analysis of 15 studies with 4024 cases and 6022 controls [51].

The rs174538 and rs4246215 polymorphisms are located in the FEN1 promoter c._69G > A and rs4246215 3′-untranslational region c.4150G4T, respectively. These two SNPs were shown to associate with decreased FEN1 expression [49]. Comet assays in 303 coke-oven works and 297 controls indicated that carriers of rs174538 variant genotypes exhibited significantly higher DNA damage levels than non-carriers. Association study with 1840 lung cancer patients and 1958 controls further revealed that these two FEN1 SNPs conferred genetic susceptibility to lung cancer [49]. Moreover, some evidence was further observed to consolidate the contribution of the rs174538 and rs4246215 to the risk of different types of cancer [25, 36, 37, 39]. Especially, these two SNPs were shown to decrease breast cancer risk in Chinese and Iran people [37] populations. The prevalence of the studied SNPs varies among different ethnic groups (data not shown). The differential distribution of allele frequencies may affect the association results, which mainly relays on genotype count of a SNP in cases and controls. Therefore, before extrapolating a finding derived from such association study in a population to another, validation study should be performed. Taken together, it is suggested that the association between SNPs and cancer risk may be affected by cancer types, ethnicities, and study sample sizes.

In contrast to genetic abnormalities, epidemiology studies regarding environmental risk factors for Wilms tumor are very few. Several epidemiology studies have proposed paternal occupational or maternal hormonal exposures during pregnancy as risk factors for Wilms tumor [5, 6, 11, 47]. However, the findings are not firm due to small numbers of participants and inconsistent exposures. A more recent study, aimed to identify perinatal risks for Wilms tumor, demonstrated the association between high fetal growth and Wilms tumor in Swedish girl under 5 years old [9]. Importantly, it also should be noted that due to short exposure time. Environmental factors probably play less important role in this early childhood tumor (the median age of 3.5 years at diagnosis) than in adult tumors.

This is a pioneer study concerning the association of BER polymorphism and Wilms tumor risk. We found three out of 18 SNPs were associated with Wilms tumor susceptibility. Our finding should be interpreted cautiously. The current study demonstrated the association between the studied SNPs and Wilms tumor, but not necessarily real causality; the latter needs to be verified by in vitro and in vivo functional analysis that provide evidence of the biological significance of this discovery in the future. Several other limitations should also be stated in this study. First, given the relatively small sample size and established association with the pediatric nephrogenic cancer, our findings called for more validations by different research groups. Second, BER gene mutation, copy number alteration, and amplification were not investigated in patients. Failure to consider such genetic abnormalities was one of limitations of this study. Third, the effects of gene-environment interactions were lacking.

In conclusion, we found that hOGG1 rs1052133, FEN1 rs174538, and rs4246215 polymorphisms may have potential protective effects on Wilms tumor. eQTL further provide biological supporting for potential
function of the significant SNPs. However, our findings should be validated in large studies and different ethnicities.

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**Conflict of Interest Disclosures**

The authors declare no competing financial interests.

**Authorship Contributions**

J. Zhu, W. Jia, J. He and G. Liu designed and performed the study and wrote the manuscript; W. Fu, W. Jia, and H. Xia collected the samples and information; J. Zhu, C. Wu, and J. He participated in analyzing data; W. Fu, J. He and G. Liu coordinated the study over the entire time. All authors reviewed the final manuscript.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.06.018.

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