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Research Paper

Functional Polymorphisms at *ERCC1/XPF* Genes Confer Neuroblastoma Risk in Chinese Children

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ABSTRACT

Variations in nucleotide excision repair pathway genes may predispose to initiation of cancers. However, polymorphisms of *ERCC1/XPF* genes and neuroblastoma risk have not been investigated before. To evaluate the relevance of polymorphisms of *ERCC1/XPF* genes in influencing neuroblastoma susceptibility, we genotyped four polymorphisms in *ERCC1/XPF* genes using a Chinese population of 393 cases and 812 controls. The results showed that *ERCC1* rs2298881 and rs11615 predisposed to enhanced neuroblastoma risk [CA vs. AA: adjusted odds ratio (OR) = 1.94, 95% confidence interval (CI) = 1.30–2.89, $P = 0.0012$; CC vs. AA: adjusted OR = 2.18, 95% CI = 1.45–3.26, $P = 0.0002$ for rs2298881, and AG vs. GG: adjusted OR = 1.31, 95% CI = 1.02–1.69, $P = 0.038$ for rs11615]. Moreover, *XPF* rs2276466 was also associated with increased neuroblastoma risk (GG vs. CC: adjusted OR = 1.66, 95% CI = 1.02–2.71, $P = 0.043$). In the combined analysis of *ERCC1*, we found that carriers with 2–3 risk genotypes were more likely to get risk of neuroblastoma, when compared to those with 0–1 risk genotype (adjusted OR = 1.75; 95% CI = 1.25–2.45, $P = 0.0012$). Our study indicates that common genetic variations in *ERCC1/XPF* genes predispose to neuroblastoma risk, which needs to be further validated by ongoing efforts.

1. Introduction

Neuroblastoma, a heterogeneous tumor developed from neural crest progenitor cells, is the most common solid neoplasm of childhood (Matthay et al., 2016). Neuroblastoma takes up nearly 10% of all childhood cancers, yet its proportion of all pediatric oncology deaths is up to 15% (Cheung and Dyer, 2013). Neuroblastoma is characterized by wide clinical course, with some patients having spontaneous regression without chemotherapy or some having poor prognosis despite intense multi-modal therapy (Maris et al., 2007; Maris, 2010). In general, neuroblastoma cases can be classified into low-, intermediate-, and high-risk groups (Shimada et al., 1999). Nearly 50% of all the neuroblastoma patients are classified into high-risk group, and their survival rates are less than 40% despite intense multi-modal therapy (Matthay et al., 2016). Such unfavorable prognosis was mainly attributed to the extensive metastasis of tumor at the time of diagnosis (Matthay et al., 2016; Esposito et al., 2017).

According to the germline mutations, neuroblastoma is divided into familial and sporadic types. Familial neuroblastoma is rare, with approximately 1–2% of all neuroblastoma cases. The genetic etiology of familial neuroblastoma is relatively elucidated, that is the highly mutations in *PHOX2B* (Mosse et al., 2004; Bourdeaut et al., 2005) or *ALK* gene (Devoto et al., 2011). However, the genetic events predisposing individuals to sporadic neuroblastoma, the most common neuroblastoma, remains unclear. Previous studies indicated that environmental factors such as pregnancy exposures, dwelling condition, and dietary habit are potential risks of sporadic neuroblastoma (Cook et al., 2004; Menegaux et al., 2004; Muller-Schulte et al., 2017), yet there still lacks direct linkage evidence. Mounting evidence has suggested that genetic factors also influence the occurrence of neuroblastoma (Yang et al., 2017; Zhang et al., 2017). For example, common variants of *NEFL* and *CNKN1B* could influence neuroblastoma susceptibility (Capasso et al., 2014; Capasso et al., 2017).

Recent genome-wide association studies (GWASs) have identified genetic variants located in several genes (*HACE1*, *LIN28B*, *BARD1*, *CASC15*, *TP53*, and *LMO1*) associated with neuroblastoma risk by

Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism; NER, nucleotide excision repair; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; eQTL, expression quantitative trait loci.

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comparing neuroblastoma patients to healthy controls (Maris et al., 2008; Capasso et al., 2009; Nguyen le et al., 2011; Wang et al., 2011; Diskin et al., 2012; Diskin et al., 2014). Moreover, the role of most of these GWAS-identified single nucleotide polymorphisms (SNPs) in neuroblastoma risk have been confirmed in replication case-control studies (He et al., 2016b; He et al., 2016c; Zhang et al., 2016; He et al., 2017; Zhang et al., 2017). However, these identified genetic variations still account for only a small proportion in predisposing to neuroblastoma.

Therefore, additional gene polymorphisms associated with neuroblastoma susceptibility are needed to be identified. Due to the adoption of the multiple testing correction in the GWAS analysis, some potential SNPs might only have modest risk effects or just be omitted (Stadler et al., 2010). Thus, other research strategies were developed, which include: replication of GWAS-identified SNPs, meta-analysis of GWAS datasets, imputation and epistasis analysis, gene- or pathway-based approaches (Gao, 2011).

In human, DNA repair systems play critical roles in maintaining the stability of cellular functions and genomic integrity (Wood et al., 2001). The nucleotide excision repair (NER) pathway, one of the DNA repair systems, is responsible for excising bulky DNA lesions (Gillet and Scharer, 2006). The NER pathway includes four steps: damage recognition, DNA unwinding, damage excision, and ligation (Friedberg, 2001; Christmann et al., 2003). The eight main members of the NER process, *XPA-XPG* and *XP-V*, are all implicated in maintaining genomic integrity (Cleaver, 2000). The *ERCC1* and *XPF* (also known as *ERCC4*) genes encode proteins that participate in the DNA repair pathways. These two proteins, ERCC1 and XPF, form a heterodimeric complex to cleave the DNA damage on the 5′ side of bubble structures (Sijbers et al., 1996; Evans et al., 1997). Moreover, this complex also functions in the inter-strand crosslink repair (Wood, 2010). Owing to the critical role of ERCC1/XPF complex in maintaining genomic stability, it remains a hot spot of research to explore the role of *ERCC1/XPF* genes variations in cancer risks. To date, epidemiological studies declared that *ERCC1/XPF* genes polymorphisms were associated with cancer risk at different sites, including colorectal cancer (Yang et al., 2015), breast cancer (Yang et al., 2013), gastric cancer (He et al., 2012b), and endometrial cancer (Doherty et al., 2011).

However, the genetic variants driving the *ERCC1/XPF* genetic association with the risk of neuroblastoma has been evaluated in few instances. To determine whether *ERCC1/XPF* genes variations could predispose to neuroblastoma risk or not, we conducted a case-control study in Chinese population.

2. Materials and Methods

2.1. Study Population

This study encompassed 393 cases with neuroblastoma and 812 healthy controls of Chinese origin (He et al., 2018; Zhang et al., 2018). Among them, 275 cases were from Guangzhou Women and Children's Medical Center and 118 were from The First Affiliated Hospital of Zhengzhou University (**Supplemental Table 1**). At the same time, 531 and 281 controls were recruited from the same district, respectively. Additional details and eligibility criteria for subject selection were reported previously (He et al., 2017). All participants or their guardians provided informed consent before the research. The details of the included subjects have been described in our previous publications (He et al., 2016a; Zhang et al., 2017). The study protocols were approved by the Institutional Review Board of Guangzhou Women and Children's Medical Center, and The First Affiliated Hospital of Zhengzhou University.

2.2. SNP Selection and Genotyping

We identified potentially functional SNPs of *ERCC1/XPF* genes from dbSNP database (http://www.ncbi.nlm.nih.gov/) and an online tool, SNPinfo (http://snpinfo.niehs.nih.gov/). Briefly, we searched the potentially functional candidate SNPs located in the 5′- flanking region, 5′ untranslated region, 3′ untranslated region, and exon of *ERCC1/XPF* genes. Additional selection criteria were reported in our previous study (He et al., 2012a). In final, three SNPs (rs2298881, rs3212986, rs11615) with low linkage disequilibrium in the *ERCC1* gene (**Supplemental Fig. 1**, **Supplemental Table 2**) and one SNP (rs2276466) in the *XPF* gene (**Supplemental Table 3**) met the selection criteria. We used TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China) to extract genomic DNA from peripheral blood donated by subjects. All the selected SNPs were genotyped on a standard commercial TaqMan real-time PCR, with details reported elsewhere (Gong et al., 2017; Li et al., 2017; Lou et al., 2017). As a quality control, eight negative controls with water and eight replicate samples were included in each 384-well plate. Moreover, we randomly selected 10% of the samples to a second run. All duplicate sets had a concordance rate of 100%.

2.3. Statistical Analysis

First, we applied goodness-of-fit χ^2 test to determine whether the selected SNPs among controls were deviated from Hardy-Weinberg equilibrium (HWE). Then we adopted two-sided chi-square test to measure the difference of the demographic variables and allele frequencies between all cases and controls. We also calculated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analysis. All statistical analyses were performed using the version 9.4 SAS software (SAS Institute, Cary, NC). All the *P* values were two sided, and *P* values less than 0.05 considered as significant.

2.4. SNP-gene Expression Correlation Analysis

We performed genotype and mRNA expression correlation analysis, using genotyping data from the HapMap phase II release 23 data set and mRNA expression data by genotypes from EBV-transformed B lymphoblastoid cell lines from the same 270 HapMap individuals (He et al., 2012a). We also performed the expression quantitative trait loci (eQTL) analysis using GTEx portal web site (http://www.gtexportal.org/home/) to predict potential associations between the SNPs and gene expression levels (Consortium, 2013).

3. Results

3.1. ERCC1 and XPF Genes Polymorphisms With Neuroblastoma Susceptibility

The detailed characteristics of all the subjects were presented in **Supplemental Table 1** and in our previously published articles (He et al., 2018; Zhang et al., 2018). The distribution of *ERCC1/XPF* genes polymorphisms between all cases and controls were listed in Table 1. In analysis of neuroblastoma patients and controls, three SNPs (two in *ERCC1* and one in *XPF*) were associated with neuroblastoma risk: rs2298881 in *ERCC1* (CA vs. AA: adjusted OR = 1.94, 95% CI = 1.30–2.89, $P = 0.0012$; CC vs. AA: adjusted OR = 2.18, 95% CI = 1.45–3.26, $P = 0.0002$); rs11615 in *ERCC1* (AG vs. GG: adjusted OR = 1.31, 95% CI = 1.02–1.69, $P = 0.038$); and rs2276466 in *XPF* (GG vs. CC: adjusted OR = 1.66, 95% CI = 1.02–2.71, $P = 0.043$). However, we failed to detect a statistically significant relationship between rs3212986 in *ERCC1* and neuroblastoma risk. Higher risk of neuroblastoma was found in individuals with 2–3 combined risk genotypes of *ERCC1*, compared with those with 0–1 risk genotypes (adjusted OR = 1.75; 95% CI = 1.25–2.45, $P = 0.0012$).

3.2. Stratification Analysis

We further evaluated the effects of the selected polymorphisms on the neuroblastoma risk among different strata including age, gender,

Table 1
Logistic regression analysis for the correlation of *ERCC1* and *XPF* polymorphisms with neuroblastoma risk.

Genotype	Cases (N = 393)	Controls (N = 812)	P[a]	Crude OR (95% CI)	P	Adjusted OR (95% CI) [b]	P[b]
rs2298881 (HWE = 0.060)							
AA	38 (9.67)	145 (17.86)		1.00		1.00	
CA	184 (46.82)	365 (44.95)		**1.92 (1.29–2.87)**	**0.0013**	**1.94 (1.30–2.89)**	**0.0012**
CC	171 (43.51)	302 (37.19)		**2.16 (1.44–3.23)**	**0.0002**	**2.18 (1.45–3.26)**	**0.0002**
Additive			**0.0007**	**1.36 (1.14–1.62)**	**0.0007**	**1.36 (1.14–1.62)**	**0.0007**
Dominant	355 (90.33)	667 (82.14)	**0.0002**	**2.03 (1.39–2.97)**	**0.0003**	**2.05 (1.40–2.99)**	**0.0002**
Recessive	222 (56.49)	510 (62.81)	**0.035**	**1.30 (1.02–1.66)**	**0.035**	**1.30 (1.02–1.66)**	**0.035**
rs3212986 (HWE = 0.193)							
CC	166 (42.24)	372 (45.81)		1.00		1.00	
CA	180 (45.80)	343 (42.24)		1.18 (0.91–1.52)	0.216	1.18 (0.91–1.52)	0.210
AA	47 (11.96)	97 (11.95)		1.09 (0.73–1.61)	0.682	1.09 (0.73–1.61)	0.676
Additive			0.465	1.08 (0.91–1.29)	0.389	1.08 (0.91–1.29)	0.382
Dominant	227 (57.76)	440 (54.19)	0.242	1.16 (0.91–1.47)	0.242	1.16 (0.91–1.48)	0.236
Recessive	346 (88.04)	715 (88.05)	0.995	1.00 (0.69–1.45)	0.995	1.00 (0.69–1.45)	0.992
rs11615 (HWE = 0.035)							
GG	209 (53.18)	482 (59.36)		1.00		1.00	
GA	155 (39.44)	273 (33.62)		**1.31 (1.01–1.69)**	**0.039**	**1.31 (1.02–1.69)**	**0.038**
AA	29 (7.38)	57 (7.02)		1.17 (0.73–1.89)	0.510	1.18 (0.73–1.89)	0.502
Additive			0.114	1.18 (0.98–1.43)	0.090	1.18 (0.98–1.43)	0.088
Dominant	184 (46.82)	330 (40.64)	**0.042**	**1.29 (1.01–1.64)**	**0.042**	**1.29 (1.01–1.64)**	**0.042**
Recessive	364 (92.62)	755 (92.98)	0.820	1.06 (0.66–1.68)	0.819	1.06 (0.67–1.68)	0.812
rs2276466 (HWE = 0.544)							
CC	230 (59.43)	478 (58.87)		1.00		1.00	
CG	125 (32.30)	294 (36.21)		0.88 (0.68–1.14)	0.337	0.88 (0.68–1.15)	0.345
GG	32 (8.27)	40 (4.93)		**1.66 (1.01–2.70)**	**0.044**	**1.66 (1.02–2.71)**	**0.043**
Additive			**0.049**	1.08 (0.88–1.31)	0.459	1.08 (0.89–1.32)	0.452
Dominant	157 (40.57)	334 (41.13)	0.853	0.98 (0.76–1.25)	0.853	0.98 (0.77–1.25)	0.862
Recessive	355 (91.73)	772 (95.07)	**0.023**	**1.74 (1.08–2.82)**	**0.024**	**1.74 (1.08–2.82)**	**0.024**
Combined effect of risk genotypes for *ERCC1* [c]							
0	38 (9.67)	142 (17.49)	**0.005** [d]	1.00		1.00	
1	14 (3.56)	28 (3.45)		1.87 (0.90–3.90)	0.095	1.88 (0.90–3.91)	0.093
2	271 (68.96)	517 (63.67)		**1.96 (1.33–2.88)**	**0.0007**	**1.97 (1.34–2.91)**	**0.0006**
3	70 (17.81)	125 (15.39)		**2.09 (1.32–3.32)**	**0.0017**	**2.11 (1.33–3.35)**	**0.0016**
0–1	52 (13.23)	170 (20.94)		1.00		1.00	
2–3	341 (86.77)	642 (79.06)	**0.0012**	**1.74 (1.24–2.43)**	**0.0013**	**1.75 (1.25–2.45)**	**0.0012**

The results were in bold if the 95% CI excluded 1 or $P < 0.05$.
[a] χ^2 test for genotype distributions between neuroblastoma cases and controls.
[b] Adjusted for age and gender.
[c] Risk genotypes were rs2298881 CA/CC, rs3212986 CA/AA and rs11615 GA/AA.
[d] For additive model.

tumor sites of origin and clinical stages. The conferring increased neuroblastoma risk of rs2298881 variant AC/CC genotypes was more evident in subgroups of age > 18 months (adjusted OR = 2.26, 95% CI = 1.44–3.56, $P = 0.0004$), female (adjusted OR = 2.15, 95% CI = 1.18–3.92, $P = 0.012$), male (adjusted OR = 1.98, 95% CI = 1.21–3.24, $P = 0.007$), tumor in retroperitoneal (adjusted OR = 4.47, 95% CI =

Table 2
Stratification analysis for the association between *ERCC1* gene genotypes and neuroblastoma susceptibility.

Variables	rs2298881 (case/control)		Adjusted OR[a] (95% CI)	P[a]	rs11615 (case/control)		Adjusted OR[a] (95% CI)	P[a]	Risk genotypes (case/control)		Adjusted OR[a] (95% CI)	P[a]
	AA	CA/CC			GG	GA/AA			0–1	2–3		
Age, month												
≤18	15/42	115/263	1.67 (0.83–3.36)	0.151	61/182	65/123	**1.58 (1.04–2.39)**	**0.033**	17/50	109/255	1.26 (0.69–2.28)	0.450
>18	27/103	240/404	**2.26 (1.44–3.56)**	**0.0004**	148/300	119/207	1.16 (0.86–1.57)	0.327	35/120	232/387	**2.05 (1.36–3.09)**	**0.0006**
Gender												
Female	15/60	153/282	**2.15 (1.18–3.92)**	**0.012**	86/196	82/146	1.28 (0.88–1.86)	0.192	22/67	146/275	1.61 (0.95–2.71)	0.076
Male	23/85	202/385	**1.98 (1.21–3.24)**	**0.007**	123/286	102/184	1.30 (0.94–1.79)	0.111	30/103	195/367	**1.86 (1.19–2.90)**	**0.006**
Sites of origin												
Adrenal gland	19/145	134/667	1.60 (0.96–2.68)	0.074	90/482	63/330	1.03 (0.73–1.47)	0.854	26/170	127/642	1.35 (0.85–2.13)	0.203
Retroperitoneal	4/145	83/667	**4.47 (1.61–12.40)**	**0.004**	37/482	50/330	**1.99 (1.27–3.12)**	**0.003**	4/170	83/642	**5.49 (1.98–15.20)**	**0.001**
Mediastinum	9/145	100/667	**2.37 (1.17–4.81)**	**0.017**	57/482	52/330	1.32 (0.88–1.97)	0.176	15/170	94/642	1.63 (0.92–2.88)	0.096
Others	5/145	31/667	1.31 (0.50–3.43)	0.587	21/482	15/330	1.04 (0.53–2.05)	0.910	5/170	31/642	1.60 (0.61–4.19)	0.340
Clinical stage												
I + II + 4 s	19/145	143/667	1.61 (0.97–2.69)	0.067	90/482	72/330	1.16 (0.82–1.63)	0.398	22/170	140/642	**1.65 (1.02–2.68)**	**0.041**
III + IV	18/145	193/667	**2.45 (1.46–4.11)**	**0.0007**	110/482	101/330	1.35 (1.00–1.84)	0.053	29/170	182/642	**1.73 (1.13–2.65)**	**0.013**

The results were in bold if the 95% CI excluded 1 or $P < 0.05$.
[a] Adjusted for age and gender, omitting the corresponding stratification factor.

1.61–12.40, $P = 0.004$), tumor in mediastinum (adjusted OR = 2.37, 95% CI = 1.17–4.81, $P = 0.017$) and clinical stage III + IV (adjusted OR = 2.45, 95% CI = 1.46–4.11, $P = 0.0007$). The rs11615 GA/AA was associated with an increased risk of neuroblastoma, particularly in subgroups of age ≤ 18 (adjusted OR = 1.58, 95% CI = 1.04–2.39, $P = 0.033$), tumor in retroperitoneal (adjusted OR = 1.99, 95% CI = 1.27–3.12, $P = 0.003$), compared with the homozygous wild-type genotype. After combining risk genotypes, we observed that the patients carrying 2–3 risk genotypes had a more evident risk in age > 18 (adjusted OR = 2.05, 95% CI = 1.36–3.09, $P = 0.0006$), males (adjusted OR = 1.86, 95% CI = 1.19–2.90, $P = 0.006$), tumor in retroperitoneal (adjusted OR = 5.49, 95% CI = 1.98–15.20, $P = 0.001$), clinical stage I + II + 4 s (adjusted OR = 1.65, 95% CI = 1.02–2.68, $P = 0.041$) and clinical stage III + IV (adjusted OR =1.73, 95% CI = 1.13–2.65, $P = 0.013$) (Table 2).

XPF rs2276466 GG was associated with an increased risk of neuroblastoma, particularly in subgroups of age > 18 (adjusted OR = 2.21, 95% CI = 1.23–3.97, $P = 0.008$) and females (adjusted OR = 2.51, 95% CI = 1.22–5.16, $P = 0.013$), compared with the CC/CG genotype. However, we failed to observe significant association between *XPF* rs2276466 and neuroblastoma risk under the rest of the evaluated subgroups (Table 3).

3.3. Genotype and mRNA Expression Correlation Analysis

We observed that *ERCC1* mRNA expression levels in rs2298881 CC and AC/CC genotypes carriers were significantly enhanced when compared to the AA genotype carriers in Chinese, Africans, and the overall population (Table 4). We also detected a higher *ERCC1* mRNA expression level for rs3212986 AA genotypes for Europeans ($P = 0.026$) and rs3212986 AC genotype for African ($P = 0.046$). As to the rs2276466 polymorphism in *ERCC4*, the mRNA expression level was upregulated in GG genotype in Europeans ($P = 0.035$) and the overall populations ($P = 0.021$) (Table 4). More specifically, the mRNA expression level of 45 cell lines from Chinese (Fig. 1a) was similar to that of the overall populations (Fig. 1b). As a further assessment of the putative functional relevance of *ERCC1* rs2298881 and rs11615, alteration in *ERCC1* expression was seen in transformed fibroblasts tissues of individuals who carry polymorphic allele of *ERCC1* rs2298881 (Fig. 1c) and rs11615 (Fig. 1d) based on the public database GTEx portal.

Table 3
Stratification analysis for the association between *XPF* rs2276466 C>G polymorphism and neuroblastoma susceptibility.

Variables	CC/CG (Cases/controls)	GG (Cases/controls)	Crude OR (95% CI)	*P*	Adjusted OR[a] (95% CI)	*P*[a]
Age, month						
≤18	117/288	7/17	1.01 (0.41–2.51)	0.977	1.01 (0.41–2.51)	0.978
>18	238/484	25/23	**2.21 (1.23–3.98)**	**0.008**	**2.21 (1.23–3.97)**	**0.008**
Gender						
Females	149/327	17/15	**2.49 (1.21–5.11)**	**0.013**	**2.51 (1.22–5.16)**	**0.013**
Males	206/445	15/25	1.30 (0.67–2.51)	0.442	1.32 (0.68–2.56)	0.410
Sites of origin						
Adrenal gland	143/772	9/40	1.22 (0.58–2.56)	0.609	1.25 (0.59–2.64)	0.558
Retroperitoneal	75/772	7/40	1.80 (0.78–4.16)	0.168	1.79 (0.78–4.15)	0.172
Mediastinum	99/772	10/40	1.95 (0.95–4.02)	0.071	1.97 (0.95–4.06)	0.068
Others	33/772	3/40	1.76 (0.52–5.97)	0.368	1.71 (0.50–5.82)	0.392
Clinical stages						
I + II + 4 s	149/772	13/40	1.68 (0.88–3.23)	0.116	1.68 (0.88–3.22)	0.118
III + IV	190/772	17/40	1.73 (0.96–3.11)	0.069	1.74 (0.96–3.14)	0.067

The results were in bold if the 95% CI excluded 1 or $P < 0.05$.
[a] Adjusted for age and gender, omitting the corresponding stratification factor.

4. Discussion

To determine whether SNPs in *ERCC1/XPF* genes can predispose to neuroblastoma risk, we conducted the first case-control, hospital-based study using Chinese children. Our data revealed that the rs2298881 and rs11615 in *ERCC1* as well as rs2276466 in *XPF* exhibited significant positive associations with neuroblastoma risk.

ERCC1 gene is located to chromosome 19q13.32 and comprises 10 exons. *XPF* is mapped to chromosome 16p13.12 and consists of 11 exons. Their encoded proteins, ERCC1 and XPF, function as a structure-specific endonuclease in a heterodimeric manner (Tsodikov et al., 2005). This heterodimer catalyzes the 5′ incision during the course of NER (Houtsmuller et al., 1999). In the ERCC1/XPF heterodimer, ERCC1 serves as a critical DNA binding subunit without endonuclease activity, whereas XPF is catalytically active (Enzlin and Scharer, 2002). It is elucidated that mutations in the *ERCC1* and *ERCC4* genes are associated with several human inherited disorders (Niedernhofer et al., 2006). The association of the *ERCC1/XPF* genes SNPs and cancer risk has been previously reported. For example, individuals carrying the *ERCC1* rs3212986 or rs11615 genotype had a marginally increased risk of colorectal cancer (Hou et al., 2014). However, in a case-control study conducted in USA, Jennifer et al. failed to provide evidences between the relationship of *ERCC1/XPF* genes polymorphisms and endometrial cancer risk (Doherty et al., 2011). The discrepancy results suggested that the same polymorphism might function differently in cancer susceptibility in different ethnicities or different cancer sites. As certain gene SNPs have different roles in certain cancer risk, it is necessary to determine the role of *ERCC1/XPF* genes SNPs in neuroblastoma risk.

Herein, we are the first to explore whether *ERCC1/XPF* genes SNPs could contribute to the susceptibility of neuroblastoma in Chinese children. The results showed that two SNPs in *ERCC1* (rs2298881 and rs11615) and rs2276466 in *XPF* predisposed to enhanced neuroblastoma risk. These results were quite similar to our previous study, which showed that *ERCC1* rs2298881 and rs11615 variant genotypes were associated with increased gastric cancer risk (He et al., 2012b). Such relationships were also observed in many other kinds of cancers in other studies (Zhang et al., 2012).

A myriad of evidence has documented that single SNP in individual gene might not have enough power to impact the risk of overall cancer (Pan et al., 2009). Somehow, the combination of several SNPs might bring about more significant effects. Therefore, we further performed combination analysis of the effect of risk genotypes. We found an increased risk for neuroblastoma in individuals with 2–3 variant *ERCC1* alleles, compared with those with 0–1 variant alleles, indicating that combinations of variant alleles within NER pathway can exhibit much stronger effect on neuroblastoma risk than the single variant. In agreement with our results, Tse et al., also found that individuals were more likely to develop esophageal adenocarcinoma, if they present with the combined four NER SNPs but not only one variant allele (Tse et al., 2008). In our previous epidemiological study conducted in other NER genes, we also observed such similar variant-dosage effect (He et al., 2016a). In the stratified analysis, we found that the increased neuroblastoma risk of rs2298881 variant AC/CC genotypes was more evident in subgroups of age > 18 months, female, male, tumor in retroperitoneal, tumor in mediastinum and clinical stage III + IV. Similar results were obtained in rs11615 GA/AA among subgroups of age ≤ 18, tumor in retroperitoneal. We also found that the patients carrying 2–3 risk genotypes had a more evident risk in age > 18, males, tumor in retroperitoneal, clinical stage I + II + 4 s and clinical stage III + IV. The conflicting results of relationship in subgroups might be attributed to limited statistical power caused by relatively small sample size. The stratification analysis of combined genotypes indicated that the

Table 4
ERCC1 and *XPF* mRNA expression by the genotypes of SNPs, using data from the HapMap[a].

Race	mRNA expression (rs2298881)					mRNA expression (rs3212986)					mRNA expression (rs11615)					mRNA expression (rs2276466)				
	Genotypes	No.	Mean ± SD	P^b	$P_{trend}{}^c$	Genotypes	No.	Mean ± SD	P^b	$P_{trend}{}^c$	Genotypes	No.	Mean ± SD	P^b	$P_{trend}{}^c$	Genotypes	No.	Mean ± SD	P^b	$P_{trend}{}^c$
CHB	AA	10	6.68 ± 0.13		**0.003**	CC	20	6.74 ± 0.13		0.442[d]	GG	29	6.73 ± 0.11		**0.044**	CC	28	6.27 ± 0.09		0.583[d]
	AC	20	6.76 ± 0.09	0.053		AC	19	6.77 ± 0.09	0.416		AG	12	6.79 ± 0.10	0.144		CG	13	6.23 ± 0.05	0.126	
	CC	15	6.81 ± 0.08	**0.006**		AA	5	6.77 ± 0.07	0.664		AA	4	6.83 ± 0.07	0.111		GG	3	6.29 ± 0.06	0.619	
	AC/CC	35	6.78 ± 0.09	**0.006**		AC/AA	24	6.77 ± 0.08	0.377		AG/AA	16	6.80 ± 0.09	0.054		CG/GG	16	6.24 ± 0.06	0.254	
JPT	AA	10	6.76 ± 0.08		0.242	CC	31	6.75 ± 0.09		0.442[d]	GG	21	6.75 ± 0.10		0.872	CC	21	6.23 ± 0.07		0.541
	AC	26	6.74 ± 0.11	0.647		AC	13	6.77 ± 0.12	0.442		AG	22	6.76 ± 0.10	0.846		CG	19	6.24 ± 0.07	0.927	
	CC	9	6.81 ± 0.07	0.118		AA	0	–	–		AA	2	6.76 ± 0.06	0.976		GG	5	6.26 ± 0.12	0.473	
	AC/CC	35	6.76 ± 0.10	0.968		AC/AA	13	6.77 ± 0.12	0.442		AG/AA	24	6.76 ± 0.10	0.848		CG/GG	24	6.24 ± 0.08	0.738	
CEU	AA	0	–		0.370	CC	52	6.77 ± 0.13		0.725	GG	6	6.85 ± 0.13		0.447	CC	54	6.34 ± 0.08		0.062[d]
	AC	11	6.74 ± 0.18	–		AC	35	6.74 ± 0.12	0.279		AG	49	6.76 ± 0.14	0.168		CG	28	6.36 ± 0.11	0.419	
	CC	79	6.77 ± 0.12	–		AA	3	6.95 ± 0.04	**0.026**		AA	35	6.77 ± 0.11	0.111		GG	7	6.42 ± 0.10	**0.035**	
	AC/CC	90	6.77 ± 0.13	–		AC/AA	38	6.76 ± 0.13	0.620		AG/AA	84	6.76 ± 0.13	0.129		CG/GG	35	6.37 ± 0.11	0.173	
YRI	AA	2	6.61 ± 0.003		<**.0001**[d]	CC	39	6.77 ± 0.10		0.208	GG	87	6.79 ± 0.10		0.137	CC	72	6.25 ± 0.08		0.220
	AC	11	6.71 ± 0.07	0.066		AC	45	6.81 ± 0.09	**0.046**		AG	3	6.71 ± 0.05	0.137		CG	17	6.28 ± 0.09	0.194	
	CC	76	6.80 ± 0.09	**0.004**		AA	6	6.76 ± 0.05	0.976		AA	0	–	–		GG	1	6.26	0.850	
	AC/CC	87	6.79 ± 0.09	**0.007**		AC/AA	51	6.80 ± 0.09	0.065		AG/AA	3	6.71 ± 0.05	0.137		CG/GG	18	6.28 ± 0.09	0.193	
All	AA	22	6.71 ± 0.11		<**.0001**[d]	CC	142	6.76 ± 0.11		0.095[d]	GG	143	6.78 ± 0.10		0.599	CC	175	6.28 ± 0.09		**0.046**[d]
	AC	68	6.74 ± 0.11	0.230		AC	112	6.78 ± 0.11	0.243		AG	86	6.76 ± 0.12	0.385		CG	77	6.29 ± 0.11	0.425	
	CC	179	6.79 ± 0.10	**0.001**		AA	14	6.80 ± 0.09	0.162		AA	41	6.77 ± 0.10	0.793		GG	16	6.34 ± 0.12	**0.021**	
	AC/CC	247	6.78 ± 0.11	**0.004**		AC/AA	126	6.78 ± 0.10	0.149		AG/AA	127	6.77 ± 0.12	0.435		CG/GG	93	6.30 ± 0.11	0.169	

The results were in bold if the $P < 0.05$.

[a] *ERCC1* and *XPF* genotyping data and mRNA expression levels for *ERCC1* and *XPF* by genotypes were obtained from the HapMap phase II release 23 data from EBV-transformed lymphoblastoid cell lines from 270 individuals, including 45 unrelated Han Chinese in Beijing (CHB).

[b] Two-side Student's *t*-test within the stratum.

[c] *P* values for the trend test of mRNA expression among 3 genotypes for each SNP from a general linear model.

[d] There were missing data because genotyping data not available.

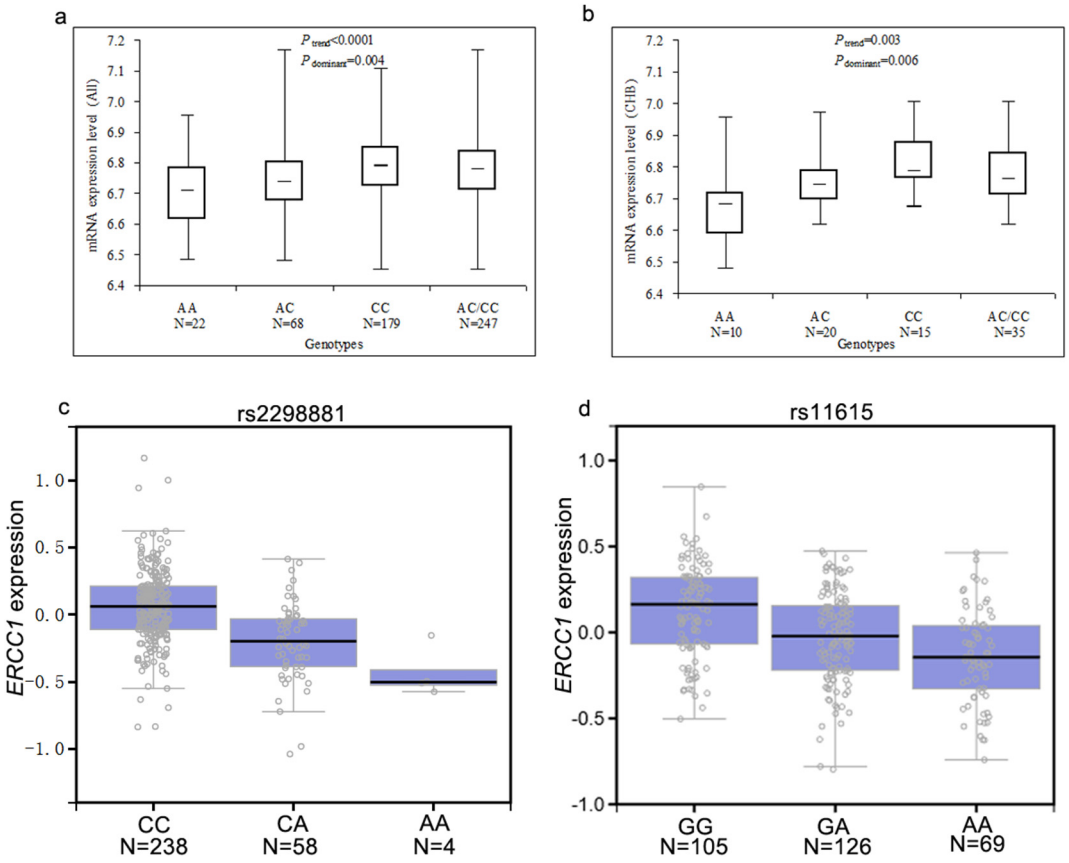

Fig. 1. Functional implication of *ERCC1* gene rs2298881 and rs11615 polymorphisms. Effect of *ERCC1* gene rs2298881 on mRNA expression in (a) 269 HapMap cell lines of all population and (b) 45 HapMap cell lines of unrelated CHB. The genotype of (c) rs2298881 and (d) rs11615 and expression of *ERCC1* gene in transformed fibroblasts tissues were searched based on the public database GTEx Portal.

contributing role of the 2–3 risk genotypes in neuroblastoma risk was similar in different clinical stages. We further adopted bioinformatic tools to explore the possible mechanisms for the SNPs showing the most significant associations. The results from HapMap data as well as eQTL analysis suggested that the increased neuroblastoma risk be associated with the upregulated expression levels of *ERCC1* and *XPF* genes. The aberrant expression of *ERCC1* and *XPF* genes might cause decreased NER repair ability, thus increased neuroblastoma risk.

Several limitations accompany with this study. First, the sample size is relative small, especially for the stratification analysis, which will impair the strength of the statistical power. Second, the risk of neuroblastoma cannot be explained only by the SNPs in *ERCC1/XPF* genes, other environmental factors also contribute to the risk of neuroblastoma. However, we cannot obtain these factors due to the nature of retrospective investigations. Third, only four SNPs in *ERCC1/XPF* genes were chosen for investigation, additional *ERCC1/XPF* genes variants contributing to neuroblastoma risk are needed to reveal. Fourth, the results should be interpreted with caution in other populations, as the population source of this study was restricted to unrelated Chinese Han ethnicity.

In summary, here we firstly provide evidence that polymorphisms in *ERCC1/XPF* genes could influence neuroblastoma risk. Ongoing epidemiological studies with additional functional analysis as well as with larger samples are needed to further elucidate how genetic variants at NER pathway influence predisposition to neuroblastoma tumorigenesis. Ultimately, our study may provide insight to the role of genetic variations in NER pathway in this aggressive pediatric tumor.

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Conflict of Interest Disclosures

The authors declare no competing financial interests.

Authors' Contributions

JH and HX designed and supervised the study. ZZ, JZ, and JH performed the experiments, analyzed the data, and wrote the paper. WL, JZ, RZ, JT, TY, YZ collected the samples and information. All authors reviewed the manuscript. In addition, all authors have read and approved the manuscript.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.03.003.

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