IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2018; 9(15): 2751-2756. doi: 10.7150/jca.25973

Research Paper

XPA gene polymorphisms and risk of neuroblastoma in Chinese children: a two-center case-control study

Jing Tao[1,#], Zhen-Jian Zhuo[2,#], Meng Su[3], Lizhao Yan[3], Jing He[4]✉, Jiao Zhang[3]✉

1. Department of Pathology, Children's Hospital Affiliated to Zhengzhou University, Henan Children's Hospital, Zhengzhou Children's Hospital, Zhengzhou 450053, Henan, China
2. School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong 999077, China
3. Department of Pediatric Surgery, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China
4. Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China

[#] These authors contributed equally to this work.

✉ Corresponding authors: Jiao Zhang, Department of Pediatric Surgery, the First Affiliated Hospital of Zhengzhou University, 1 East Jianshe Road, Zhengzhou 450052, Henan, China, Tel./Fax: (+86- 0371) 66279071, Email: zhangjiaomail@126.com; or Jing He, Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou 510623, Guangdong, China, Tel./Fax: (+86-020) 38076560, Email: hejing@gwcmc.org.

Received: 2018.03.09; Accepted: 2018.06.09; Published: 2018.07.01

Abstract

Neuroblastoma is a malignant tumor arising from the developing sympathetic nervous system, which mainly affects children. Variations in *XPA* gene have been shown to confer cancer susceptibility. However, no investigation has been reported regarding the association between *XPA* polymorphisms and neuroblastoma risk. This study was conducted to measure the association of *XPA* polymorphisms with neuroblastoma susceptibility in Chinese children. In this hospital-based case-control study with 393 cases and 812 controls, we genotyped two polymorphisms (rs1800975 T>C, and rs3176752 G>T) in *XPA* gene to access their contributions to neuroblastoma risk by TaqMan methods. The strength of the association with neuroblastoma risk was estimated by odds ratios (ORs) and 95% confidence intervals (CIs). No single polymorphism was found to predispose to neuroblastoma susceptibility. When risk genotypes were combined, we found that carriers of 1-2 risk genotypes had significantly increased neuroblastoma risk (adjusted OR=1.28; 95% CI=1.001-1.64, *P*=0.049), when compared to non-carriers. Stratification analysis by age, gender, sites of origin and clinical stages failed to show any significant association. Our study provides cues that *XPA* gene polymorphisms may exert a weak effect in neuroblastoma risk. This finding needs further validations by larger sample size studies.

Key words: neuroblastoma; *XPA*; polymorphism; susceptibility

Introduction

Neuroblastoma, a solid cancer originating from neural crest progenitor cells, is one of the most common tumors in children [1]. The median age at diagnosis of neuroblastoma is about 17 months. Neuroblastoma accounts for approximately 10% of all pediatric cancers, yet its proportion of all pediatric cancer mortality accounts for up to 15% [2]. The incidence rate of neuroblastoma in China is about 1 out of 13,000 [3]. In contrast, America witnesses is much higher, nearly 1 out of 7000 [4]. Neuroblastoma is characterized by high heterogeneity in its clinical phenotypes and symptoms [5]. Based on the clinical, pathologic, and prognostic factors, neuroblastoma cases are generally classified into low-, intermediate-, high- and ultra-high-risk groups [6]. Among them, high- and ultra-high-risk groups constitute around 50% of all cases. The outcome of these high- and ultra-high-risk groups are poor, with less than 40% cases achieving long-term survival [1]. Poor prognosis was mainly attributed to the widespread metastasis of tumor at the time of diagnosis [7, 8].

Approximately 1-2% of all cases of neuroblastoma are familial [5]. Using large-scale genetic linkage studies, several candidate predisposition chromosomal regions (2p, 12p, and 16p) have been found to associate with familial neuroblastoma risk [9, 10]. These findings further led to the discovery of certain gene mutations. Most of the familial cases have highly penetrant mutations in *PHOX2B* [11, 12] and *ALK* gene [13]. However, the underlying etiology of sporadic neuroblastoma, the most common form, remains to be elucidated. Although environmental factors such as the conception and pregnancy exposures are potential risk of sporadic neuroblastoma, direct link between has not yet been established [14, 15].

Expanding body of evidence has suggested that genetic factors and genetic-environmental interactions could contribute to the susceptibility of neuroblastoma. Recent genome-wide association studies (GWASs) have identified several neuroblastoma susceptibility loci, including single nucleotide polymorphisms (SNPs) in *HACE1*, *LIN28B*, *BARD1*, *CASC15*, *TP53*, and *LMO1* [16-21]. The association of neuroblastoma risk with *LMO1*, *BARD1*, *LIN28B*, and *TP53* polymorphisms have been confirmed in many replication case-control studies [22-26]. Another powerful way to investigate the role of gene polymorphisms in cancer risk is to analyze the genetic linkage between potential functional SNPs in core genes and cancer susceptibility. This method could overcome the limitation of GWAS, as most of the GWAS-identified SNPs only have modest risk effects due to the adoption of restricted *P*-value (1×10^5) [27]. Therefore, additional neuroblastoma susceptibility loci or gene polymorphisms are warranted to be identified.

The stability of cellular functions and genomic integrity is primarily maintained by DNA repair systems [28]. Among the various DNA repair systems, the nucleotide excision repair (NER) pathway is responsible for excising bulky DNA lesions [29]. A myriad of evidences have proven that defects in NER pathway might weaken the DNA repair capacity and thus predispose to cancer risks [30]. The NER process mainly consists of four steps: damage recognition, unwinding of the DNA, removal of the damage, and ligation [31, 32]. Eight critical genes (*XPA*-*XPG* and *ERCC1*) participate in the repair process and coordinately maintain genomic integrity [33]. *XPA* (*xeroderma pigmentosum complementary group A*) gene encodes a zinc finger DNA binding protein. This DNA binding-protein, XPA, is essential in organizing the DNA damage site and then functioning as a scaffold to excise lesions [34, 35]. Owing to the important role of XPA protein in NER pathway, the association between *XPA* polymorphisms and cancer risk remains a hot spot of research. By now, several epidemiological studies have been performed to determine of the association with the risk of cancer, including colorectal cancer [36], laryngeal cancer [37], lung cancer [38], and B-cell lymphoma [39].

Because of the universal importance of XPA in cancer, we conducted a case-control study to determine whether the SNPs in *XPA* gene could predispose to neuroblastoma in Chinese population.

Materials and methods

Study subjects

Totally, 393 cases with neuroblastoma and 812 healthy controls were recruited in this hospital-based epidemiological study [40-42]. To be specific, 275 cases and 531 controls were from Guangzhou Women and Children's Medical Center and the rest were from The First Affiliated Hospital of Zhengzhou University [25, 43, 44]. All the participants were unrelated Chinese Han children. Written informed consent was provided before the study by all participants or their guardians. The study protocols obtained approval from the Institutional Review Board of Guangzhou Women and Children's Medical Center and the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University.

SNP selection and genotyping

We chose potentially functional polymorphisms of *XPA* gene from dbSNP database (http://www.ncbi.nlm.nih.gov/) and an online tool, SNPinfo (http:// snpinfo.niehs.nih.gov/) using the selection criteria described in our published studies [45]. Two SNPs (rs1800975 T>C, and rs3176752 G>T) in the *XPA* gene were selected in the final analysis. In them, rs1800975 T>C might affect transcription activity, while rs3176752 G>T might affect the microRNA binding site activity. Genomic DNA was extracted from peripheral blood donated by all the included subjects using a TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China). TaqMan real-time PCR was performed to genotype the selected SNPs. The details of genotyping protocol could be obtained in previous studies [46-49]. As a quality control, 10% of the random samples were carried out twice. A concordance rate of 100% was got for all duplicate sets.

Statistical analysis

First, deviation from Hardy-Weinberg equilibrium (HWE) of the selected SNPs among controls was assessed by goodness-of-fit χ^2 test. Two-sided chi-squared test was used to identify the difference of the demographic variables and allele frequencies between the cases and controls. Logistic

regression analysis, served to provide odds ratios (ORs) and 95% confidence intervals (CIs), was adopted to estimate the association between *XPA* SNPs and neuroblastoma risk. Significance was achieved when *P* values were less than 0.05. All statistical analyses were performed using the version 9.4 SAS statistical package (SAS Institute, Cary, NC).

Results

Correlation of XPA gene polymorphisms with neuroblastoma susceptibility

The detailed characteristics of all the cases and controls could be found in our previously published articles [40-42]. In brief, no statistically significant differences were found between cases and controls regarding age (P>0.05) and gender (P>0.05). According to the INSS criteria, 69 (17.56%), 93 (23.66%), 68 (17.30%), 143 (36.39%), and 11 (2.80%) patients were diagnosed with clinical stages I, II, III, IV, and 4s disease, respectively. In terms of tumor sites, 153 (38.93%) neuroblastomas occurred in the adrenal glands, 109 (27.74%) in the mediastinum, 87 (22.14%) in retroperitoneal regions, and 36 (9.16%) in other regions. To evaluate the relationship between these two SNPs as well as the combined risk genotypes of *XPA* gene (rs1800975 T>C, rs3176752 G>T) and risk of neuroblastoma, crude and adjusted ORs and their 95% CIs were calculated. The main results of the above calculations were listed in **Table 1**. In general, we failed to detect any statistically significant differences in the genotype frequencies distribution of rs1800975 T>C or rs3176752 G>T polymorphism. Moreover, none of the two polymorphisms were significantly associated with neuroblastoma risk. The allele frequencies for controls in both rs1800975 and rs3176752 genotypes were in Hardy-Weinberg equilibrium, with P values equal to 0.068 and 0.416, respectively. Further analysis of the combined effect of risk genotypes revealed that 1-2 combined risk genotypes was markedly associated with an increased risk of neuroblastoma, compared with those without any risk genotypes (adjusted OR=1.28; 95% CI=1.001-1.64, P=0.049).

Stratification analysis of XPA gene polymorphisms with neuroblastoma susceptibility

We further conducted subgroup analyses by age, gender, tumor sites of origin and clinical stages to evaluate the contributions of the selected polymorphisms and their combined risk genotypes to the risk of neuroblastoma (**Table 2**). However, the calculated results indicated that there lacks significant difference association between the selected polymorphisms as well as their combined risk genotypes and neuroblastoma risk under any of the evaluated subgroups.

Haplotype analysis

As shown in **Table 3**, we did not find any haplotype can influence neuroblastoma susceptibility significantly.

Discussion

In order to identify the association between *XPA* SNPs and neuroblastoma risk, we conducted a two-center case-control study by recruiting 393 neuroblastoma patients and 812 healthy control subjects from Chinese population. Our results indicated that variations in *XPA* gene had no significant association with neuroblastoma risk. To the best of our knowledge, this is the first study investigating the associations in Chinese children.

XPA gene is mapped to chromosome 9p22.3. It encodes a relatively small 273-residue protein without enzymatic activity. Alternatively, XPA functions as a scaffold by interacting with many other NER proteins such as replication protein A, transcription factor IIH and excision repair cross complementing group 1-xeroderma pigmentosum group F protein complex [50]. Through interacting with these proteins, XPA protein facilitates the formation of the assembly and structural organization of human NER incision complexes [51]. Current evidence indicates that mutations in *XPA* gene impairs normal function of NER [51]. Thus, it is biologically reasonable that functional *XPA* gene variants may influence the DNA repair capacity, and thereby modify cancer risk. A vast number of studies has been performed to investigate the association of *XPA* gene SNPs with cancer risk. For example, the rs1800975 T>C polymerphism of *XPA* gene has been reported to be associated with increased risk of colorectal cancer in a study conducted in Poland [36]. Another study conducted in Norway indicated that *XPA* gene rs1800975 T>C was associated with a significant reduction in the risk of lung cancer [52]. The discrepancy results suggested that the same polymorphism might have different roles in cancer susceptibility depending on cancer sites and ethnicities, not to mention the different polymorphisms in candidate gene.

Herein, for the first time we explored whether *XPA* gene SNPs could affect neuroblastoma susceptibility in Chinese children. Unexpectedly, neither of the two polymorphisms of *XPA* gene was associated with neuroblastoma risk, in the overall analysis and stratified analysis. The null association might be partially attributed to the limited statistical power caused by relatively small sample size. Moreover, the low-penetrance of single polymorph-

ism might also account for such a null association. Neuroblastoma is a multifactorial and complex disease resulting from interplay between multiple genetic and environmental factors [1, 5, 53]. Previous study has demonstrated that polymorphisms in individual genes might not have enough impact on the risk of cancer [54]. Thus, it would be expected that the combined SNPs might have greater effects. Indeed, combined analysis revealed that 1-2 combined risk genotypes was markedly associated with an increased risk of neuroblastoma, compared with 0 risk genotypes. Consistent with our results, Tse et al. [55], found that compared with one variant allele alone, the combined four NER SNPs could significantly increase risk of esophageal adenocarcinoma. Similar variant-dosage effect was also observed in our former case-control study in other NER genes [56].

Table 1. Logistic regression analysis for the association between *XPA* gene polymorphisms and neuroblastoma susceptibility

Genotype	Cases (N=393)	Controls (N=812)	*P* [a]	Crude OR (95% CI)	*P*	Adjusted OR (95% CI) [b]	*P* [b]
rs1800975 (HWE=0.068)							
TT	111 (28.24)	191 (23.52)		1.00		1.00	
TC	197 (50.13)	432 (53.20)		0.79 (0.59-1.05)	0.099	0.79 (0.59-1.05)	0.101
CC	85 (21.63)	189 (23.28)		0.77 (0.55-1.10)	0.147	0.78 (0.55-1.10)	0.150
Additive			0.207	0.88 (0.74-1.04)	0.134	0.88 (0.74-1.04)	0.137
Dominant	282 (71.76)	621 (76.48)	0.076	0.78 (0.60-1.03)	0.077	0.78 (0.60-1.03)	0.079
Recessive	308 (78.37)	623 (76.72)	0.522	0.91 (0.68-1.22)	0.523	0.91 (0.68-1.22)	0.527
rs3176752 (HWE=0.416)							
GG	301 (76.59)	639 (78.69)		1.00		1.00	
GT	83 (21.12)	160 (19.70)		1.10 (0.82-1.48)	0.526	1.10 (0.82-1.49)	0.516
TT	9 (2.29)	13 (1.60)		1.47 (0.62-3.48)	0.381	1.47 (0.62-3.48)	0.382
Additive			0.576	1.13 (0.88-1.46)	0.331	1.14 (0.88-1.47)	0.325
Dominant	92 (23.41)	173 (21.31)	0.408	1.13 (0.85-1.51)	0.409	1.13 (0.85-1.51)	0.400
Recessive	384 (97.71)	799 (98.40)	0.402	1.44 (0.61-3.40)	0.405	1.44 (0.61-3.40)	0.407
Combine risk genotypes [c]							
0 [d]	232 (59.03)	527 (64.90)	0.132	1.00		1.00	
1 [d]	119 (30.28)	206 (25.37)		1.31 (1.00-1.73)	0.052	1.31 (1.00-1.72)	0.054
2 [d]	42 (10.69)	79 (9.73)		1.21 (0.81-1.81)	0.361	1.21 (0.81-1.82)	0.354
0	232 (59.03)	527 (64.90)		1.00		1.00	
1-2	161 (40.97)	285 (35.10)	0.048	**1.28 (1.002-1.64)**	**0.048**	**1.28 (1.001-1.64)**	**0.049**

[a] χ^2 test for genotype distributions between neuroblastoma cases and controls.
[b] Adjusted for age and gender.
[c] Risk genotypes were rs1800975 TT, and rs3176752 GT/TT.
[d] 0 was no risk genotype, 1 was rs1800975 TT or rs3176752 GT/TT, 2 was rs1800975 TT and rs3176752 GT/TT.

Table 2. Stratification analysis of *XPA* gene polymorphisms with neuroblastoma susceptibility

Variables	rs1800975 (cases/controls)		Adjusted OR [a]	*P* [a]	rs3176752 (cases/controls)		Adjusted OR [a]	*P* [a]	Risk genotypes (cases/controls)		Adjusted OR [a]	*P* [a]
	TT	TC/CC	(95% CI)		GG	GT/TT	(95% CI)		0-1	2	(95% CI)	
Age, month												
≤18	31/64	95/241	0.81 (0.50-1.33)	0.411	93/240	33/65	1.31 (0.81-2.12)	0.273	78/203	48/102	1.23 (0.80-1.89)	0.357
>18	80/127	187/380	0.78 (0.56-1.08)	0.133	208/399	59/108	1.05 (0.73-1.51)	0.782	154/324	113/183	1.31 (0.96-1.77)	0.085
Gender												
Females	43/74	125/268	0.81 (0.52-1.24)	0.324	133/268	35/74	0.94 (0.60-1.48)	0.798	104/226	64/116	1.19 (0.81-1.75)	0.364
Males	68/117	157/353	0.78 (0.55-1.11)	0.169	168/371	57/99	1.27 (0.87-1.84)	0.213	128/301	97/169	1.33 (0.96-1.84)	0.086
Sites of origin												
Adrenal gland	43/191	110/621	0.80 (0.54-1.19)	0.269	119/639	34/173	1.06 (0.70-1.61)	0.777	88/527	65/285	1.35 (0.95-1.92)	0.096
Retroperitoneal	24/191	63/621	0.80 (0.49-1.33)	0.392	68/639	19/173	1.02 (0.60-1.75)	0.931	53/527	34/285	1.19 (0.75-1.87)	0.461
Mediastinum	32/191	77/621	0.73 (0.47-1.13)	0.158	80/639	29/173	1.33 (0.84-2.10)	0.226	63/527	46/285	1.36 (0.91-2.05)	0.138
Others	10/191	26/621	0.79 (0.37-1.66)	0.528	27/639	9/173	1.22 (0.56-2.65)	0.613	22/527	14/285	1.19 (0.60-2.36)	0.624
Clinical stages												
I+II+4s	44/191	118/621	0.81 (0.55-1.19)	0.297	119/639	43/173	1.33 (0.90-1.96)	0.150	95/527	67/285	1.32 (0.93-1.86)	0.115
III+IV	64/191	147/621	0.72 (0.51-1.01)	0.055	167/639	44/173	0.98 (0.68-1.43)	0.929	123/527	88/285	1.31 (0.96-1.79)	0.089

[a] Adjusted for age and gender without the corresponding stratification factor.

Table 3. Association between inferred haplotypes of *XPA* gene and neuroblastoma susceptibility

Haplotypes [a]	Cases (N=786)	Controls (N=1624)	Crude OR (95% CI)	*P*	Adjusted OR [b] (95% CI)	*P* [b]
CG	317 (40.33)	716 (44.09)	1.00		1.00	
CT	50 (6.36)	94 (5.79)	1.20 (0.83-1.74)	0.328	1.20 (0.83-1.74)	0.328
TG	368 (46.82)	722 (44.46)	1.15 (0.96-1.38)	0.130	1.15 (0.96-1.38)	0.134
TT	51 (6.49)	92 (5.67)	1.25 (0.87-1.81)	0.230	1.26 (0.87-1.81)	0.226

[a] The haplotypes order were rs1800975 and rs3176752.
[b] Obtained in logistic regression models with adjustment for age and gender.

Although this study has its own merits, limitation accompanies. First, as a hospital-based case-control study, selection bias is inevitable. Second, the sample size of this case-control study is relatively small, especially for the stratification analysis. As a result, the statistical power was compromised. Thus, these findings call for replication studies in larger sample size. Third, the number of the analyzed SNPs is limited. Fourth, neuroblastoma is a heterogeneous disease with complex etiology; thus, genetic analysis alone is far more enough to elucidate its etiology. Yet due to the nature of retrospective investigations, we failed to obtain other risk exposing factors, such as paternal exposures, living environment, and dietary intake. Further studies including environmental factors analysis and gene-environment interaction analysis are warranted. Fifth, the conclusion obtained from this study could not be directly extrapolated to other ethnicities, as all the included subjects were restricted to unrelated Chinese Han ethnicity.

In summary, we first investigated the association of *XPA* gene polymorphisms with neuroblastoma risk. Our results indicated that no single *XPA* gene polymorphism could influence neuroblastoma risk. Ongoing epidemiological studies with larger samples from different ethnicities are needed to further elucidate the role of *XPA* gene polymorphisms in neuroblastoma tumorigenesis.

Abbreviations

GWAS, genome-wide association study; SNP, single nucleotide polymorphism; NER, nucleotide excision repair; *XPA*, *xeroderma pigmentosum complementary group A*, HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval.

Acknowledgements

This work was supported by grants from National Natural Science Foundation of China (No: 81502187), and Pearl River S&T Nova Program of Guangzhou (No: 201710010086).

Competing Interests

The authors have declared that no competing interest exists.

References

1. Matthay KK, Maris JM, Schleiermacher G, Nakagawara A, Mackall CL, Diller L, et al. Neuroblastoma. Nat Rev Dis Primers. 2016; 2: 16078.
2. Cheung NK, Dyer MA. Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer. 2013; 13: 397-411.
3. Bao PP, Li K, Wu CX, Huang ZZ, Wang CF, Xiang YM, et al. [Recent incidences and trends of childhood malignant solid tumors in Shanghai, 2002-2010]. Zhonghua Er Ke Za Zhi. 2013; 51: 288-94.
4. Gurney JG, Ross JA, Wall DA, Bleyer WA, Severson RK, Robison LL. Infant cancer in the U.S.: histology-specific incidence and trends, 1973 to 1992. J Pediatr Hematol Oncol. 1997; 19: 428-32.
5. Maris JM, Hogarty MD, Bagatell R, Cohn SL. Neuroblastoma. Lancet. 2007; 369: 2106-20.
6. Shimada H, Ambros IM, Dehner LP, Hata J, Joshi VV, Roald B, et al. The International Neuroblastoma Pathology Classification (the Shimada system). Cancer. 1999; 86: 364-72.
7. Maris JM. Recent advances in neuroblastoma. N Engl J Med. 2010; 362: 2202-11.
8. Esposito MR, Aveic S, Seydel A, Tonini GP. Neuroblastoma treatment in the post-genomic era. J Biomed Sci. 2017; 24: 14.
9. Mosse YP, Laudenslager M, Longo L, Cole KA, Wood A, Attiyeh EF, et al. Identification of ALK as a major familial neuroblastoma predisposition gene. Nature. 2008; 455: 930-5.
10. Chen Y, Takita J, Choi YL, Kato M, Ohira M, Sanada M, et al. Oncogenic mutations of ALK kinase in neuroblastoma. Nature. 2008; 455: 971-4.
11. Bourdeaut F, Trochet D, Janoueix-Lerosey I, Ribeiro A, Deville A, Coz C, et al. Germline mutations of the paired-like homeobox 2B (PHOX2B) gene in neuroblastoma. Cancer Lett. 2005; 228: 51-8.
12. Mosse YP, Laudenslager M, Khazi D, Carlisle AJ, Winter CL, Rappaport E, et al. Germline PHOX2B mutation in hereditary neuroblastoma. Am J Hum Genet. 2004; 75: 727-30.
13. Devoto M, Specchia C, Laudenslager M, Longo L, Hakonarson H, Maris J, et al. Genome-wide linkage analysis to identify genetic modifiers of ALK mutation penetrance in familial neuroblastoma. Hum Hered. 2011; 71: 135-9.
14. Cook MN, Olshan AF, Guess HA, Savitz DA, Poole C, Blatt J, et al. Maternal medication use and neuroblastoma in offspring. Am J Epidemiol. 2004; 159: 721-31.
15. Menegaux F, Olshan AF, Neglia JP, Pollock BH, Bondy ML. Day care, childhood infections, and risk of neuroblastoma. Am J Epidemiol. 2004; 159: 843-51.
16. Maris JM, Mosse YP, Bradfield JP, Hou C, Monni S, Scott RH, et al. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. N Engl J Med. 2008; 358: 2585-93.
17. Capasso M, Devoto M, Hou C, Asgharzadeh S, Glessner JT, Attiyeh EF, et al. Common variations in BARD1 influence susceptibility to high-risk neuroblastoma. Nat Genet. 2009; 41: 718-23.
18. Wang K, Diskin SJ, Zhang H, Attiyeh EF, Winter C, Hou C, et al. Integrative genomics identifies LMO1 as a neuroblastoma oncogene. Nature. 2011; 469: 216-20.
19. Nguyen le B, Diskin SJ, Capasso M, Wang K, Diamond MA, Glessner J, et al. Phenotype restricted genome-wide association study using a gene-centric approach identifies three low-risk neuroblastoma susceptibility Loci. PLoS Genet. 2011; 7: e1002026.
20. Diskin SJ, Capasso M, Schnepp RW, Cole KA, Attiyeh EF, Hou C, et al. Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma. Nat Genet. 2012; 44: 1126-30.
21. Diskin SJ, Capasso M, Diamond M, Oldridge DA, Conkrite K, Bosse KR, et al. Rare variants in TP53 and susceptibility to neuroblastoma. J Natl Cancer Inst. 2014; 106: dju047.
22. He J, Zhong W, Zeng J, Zhu J, Zhang R, Wang F, et al. LMO1 gene polymorphisms contribute to decreased neuroblastoma susceptibility in a Southern Chinese population. Oncotarget. 2016; 7: 22770-8.
23. He J, Yang T, Zhang R, Zhu J, Wang F, Zou Y, et al. Potentially functional polymorphisms in the LIN28B gene contribute to neuroblastoma susceptibility in Chinese children. J Cell Mol Med. 2016; 20: 1534-41.
24. Zhang R, Zou Y, Zhu J, Zeng X, Yang T, Wang F, et al. The Association between GWAS-identified BARD1 Gene SNPs and Neuroblastoma Susceptibility in a Southern Chinese Population. Int J Med Sci. 2016; 13: 133-8.
25. Zhang J, Lin H, Wang J, He J, Zhang D, Qin P, et al. LMO1 polymorphisms reduce neuroblastoma risk in Chinese children: a two-center case-control study. Oncotarget. 2017; 8: 65620-6.
26. He J, Wang F, Zhu J, Zhang Z, Zou Y, Zhang R, et al. The TP53 gene rs1042522 C>G polymorphism and neuroblastoma risk in Chinese children. Aging (Albany NY). 2017; 9: 852-9.
27. Stadler ZK, Thom P, Robson ME, Weitzel JN, Kauff ND, Hurley KE, et al. Genome-wide association studies of cancer. J Clin Oncol. 2010; 28: 4255-67.
28. Wood RD, Mitchell M, Sgouros J, Lindahl T. Human DNA repair genes. Science. 2001; 291: 1284-9.
29. Gillet LC, Scharer OD. Molecular mechanisms of mammalian global genome nucleotide excision repair. Chem Rev. 2006; 106: 253-76.
30. Berwick M, Vineis P. Markers of DNA repair and susceptibility to cancer in humans: an epidemiologic review. J Natl Cancer Inst. 2000; 92: 874-97.
31. Friedberg EC. How nucleotide excision repair protects against cancer. Nat Rev Cancer. 2001; 1: 22-33.
32. Christmann M, Tomicic MT, Roos WP, Kaina B. Mechanisms of human DNA repair: an update. Toxicology. 2003; 193: 3-34.
33. Cleaver JE. Common pathways for ultraviolet skin carcinogenesis in the repair and replication defective groups of xeroderma pigmentosum. J Dermatol Sci. 2000; 23: 1-11.
34. Sugitani N, Shell SM, Soss SE, Chazin WJ. Redefining the DNA-binding domain of human XPA. J Am Chem Soc. 2014; 136: 10830-3.
35. Scharer OD. Nucleotide excision repair in eukaryotes. Cold Spring Harb Perspect Biol. 2013; 5: a012609.
36. Dziki L, Dziki A, Mik M, Majsterek I, Kabzinski J. Modulation of Colorectal Cancer Risk by Polymorphisms in 51Gln/His, 64Ile/Val, and 148Asp/Glu of APEX Gene; 23Gly/Ala of XPA Gene; and 689Ser/Arg of ERCC4 Gene. Gastroenterol Res Pract. 2017; 2017: 3840243.

37. Lu B, Li J, Gao Q, Yu W, Yang Q, Li X. Laryngeal cancer risk and common single nucleotide polymorphisms in nucleotide excision repair pathway genes ERCC1, ERCC2, ERCC3, ERCC4, ERCC5 and XPA. Gene. 2014; 542: 64-8.
38. Mei C, Hou M, Guo S, Hua F, Zheng D, Xu F, et al. Polymorphisms in DNA repair genes of XRCC1, XPA, XPC, XPD and associations with lung cancer risk in Chinese people. Thorac Cancer. 2014; 5: 232-42.
39. Ruiz-Cosano J, Torres-Moreno D, Conesa-Zamora P. Influence of polymorphisms in ERCC5, XPA and MTR DNA repair and synthesis genes in B-cell lymphoma risk. A case-control study in Spanish population. J BUON. 2013; 18: 486-90.
40. He J, Zou Y, Liu X, Zhu J, Zhang J, Zhang R, et al. Association of Common Genetic Variants in Pre-microRNAs and Neuroblastoma Susceptibility: A Two-Center Study in Chinese Children. Mol Ther Nucleic Acids. 2018; 11: 1-8.
41. Zhang Z, Chang Y, Jia W, Zhang J, Zhang R, Zhu J, et al. LINC00673 rs11655237 C>T confers neuroblastoma susceptibility in Chinese population. Biosci Rep. 2018; 38: BSR20171667.
42. Zhuo ZJ, Liu W, Zhang J, Zhu J, Zhang R, Tang J, et al. Functional Polymorphisms at ERCC1/XPF Genes Confer Neuroblastoma Risk in Chinese Children. EBioMedicine. 2018; 30: 113-9.
43. Zhang J, Zhuo ZJ, Wang J, He J, Yang L, Zhang D, et al. CASC15 gene polymorphisms reduce neuroblastoma risk in Chinese children. Oncotarget. 2017; 8: 91343-9.
44. Wu Q, Zhuo ZJ, Zeng J, Zhang J, Zhu J, Zou Y, et al. Association between NEFL Gene Polymorphisms and Neuroblastoma Risk in Chinese Children: A Two-Center Case-Control Study. J Cancer. 2018; 9: 535-9.
45. He J, Qiu LX, Wang MY, Hua RX, Zhang RX, Yu HP, et al. Polymorphisms in the XPG gene and risk of gastric cancer in Chinese populations. Hum Genet. 2012; 131: 1235-44.
46. Li J, Zou L, Zhou Y, Li L, Zhu Y, Yang Y, et al. A low-frequency variant in SMAD7 modulates TGF-beta signaling and confers risk for colorectal cancer in Chinese population. Mol Carcinog. 2017; 56: 1798-807.
47. Lou J, Gong J, Ke J, Tian J, Zhang Y, Li J, et al. A functional polymorphism located at transcription factor binding sites, rs6695837 near LAMC1 gene, confers risk of colorectal cancer in Chinese populations. Carcinogenesis. 2017; 38: 177-83.
48. Gong J, Tian J, Lou J, Wang X, Ke J, Li J, et al. A polymorphic MYC response element in KBTBD11 influences colorectal cancer risk, especially in interaction with a MYC regulated SNP rs6983267. Ann Oncol. 2018; 29: 632-9.
49. Zou D, Lou J, Ke J, Mei S, Li J, Gong Y, et al. Integrative expression quantitative trait locus-based analysis of colorectal cancer identified a functional polymorphism regulating SLC22A5 expression. Eur J Cancer. 2018; 93: 1-9.
50. Ikegami T, Kuraoka I, Saijo M, Kodo N, Kyogoku Y, Morikawa K, et al. Solution structure of the DNA- and RPA-binding domain of the human repair factor XPA. Nat Struct Biol. 1998; 5: 701-6.
51. States JC, McDuffie ER, Myrand SP, McDowell M, Cleaver JE. Distribution of mutations in the human xeroderma pigmentosum group A gene and their relationships to the functional regions of the DNA damage recognition protein. Hum Mutat. 1998; 12: 103-13.
52. Zienolddiny S, Campa D, Lind H, Ryberg D, Skaug V, Stangeland L, et al. Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. Carcinogenesis. 2006; 27: 560-7.
53. Capasso M, Diskin SJ. Genetics and genomics of neuroblastoma. Cancer Treat Res. 2010; 155: 65-84.
54. Pan J, Lin J, Izzo JG, Liu Y, Xing J, Huang M, et al. Genetic susceptibility to esophageal cancer: the role of the nucleotide excision repair pathway. Carcinogenesis. 2009; 30: 785-92.
55. Tse D, Zhai R, Zhou W, Heist RS, Asomaning K, Su L, et al. Polymorphisms of the NER pathway genes, ERCC1 and XPD are associated with esophageal adenocarcinoma risk. Cancer Causes Control. 2008; 19: 1077-83.
56. He J, Wang F, Zhu J, Zhang R, Yang T, Zou Y, et al. Association of potentially functional variants in the XPG gene with neuroblastoma risk in a Chinese population. J Cell Mol Med. 2016; 20: 1481-90.