BRITISH JOURNAL OF BIOMEDICAL SCIENCE
2021, VOL. 78, NO. 3, 135–140
https://doi.org/10.1080/09674845.2020.1870308

XPG gene polymorphisms and glioma susceptibility: a two-centre case–control study

L Yuan[a†], WM Hu[b,†], K Chen[a], Q Shi[a], A Lin[c], HT Chen[c], ZJ Zhuo[c] and L Zeng[a]

[a]Department of Pathology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China; [b]Department of Pathology, Sun Yat-sen University Cancer Center, Guangzhou, China; [c]Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China

ABSTRACT

Background: Glioma, the most common tumour in children next to leukaemia, is difficult to treat, with a poor prognosis and high recurrence rate. Xeroderma pigmentosum group G (XPG) plays a key role in the nucleotide excision repair pathway, which may modulate individual susceptibility to developing cancer. We hypothesized links between *XPG* variants and glioma in children.

Methods: We tested our hypothesis in a study comparing 171 glioma cases with 228 age and sex matched controls, determining *XPG* polymorphisms rs2094258 C > T, rs751402 C > T, rs2296147 T > C, rs1047768 T > C, rs873601 G > A by standard molecular genetic methods.

Results: rs2094258 C > T was associated with a decreased glioma risk, but carrying the rs1047768 C or rs873601 A allele brought an increased risk. Subjects carrying 5 risk genotypes had a significantly increased glioma risk at an adjusted odds ratio of 1.97 (95% confidence Interval 1.26–3.08)(p = 0.003) when compared with those carrying 0–4 risk genotypes. Furthermore, children with 5 risk genotypes had a higher glioma risk when aged >60 months, were more likely to be male, and with subtypes of astrocytic tumours, and low-grade clinical stage, when compared to those with 0–4 risk genotypes. Preliminary functional exploration suggested that rs2094258 is linked with the expression of its surrounding genes in the expression quantitative trait locus analysis.

Conclusion: Certain variants of *XPG* are risk factors for paediatric glioma, and so may be useful in early diagnosis.

ARTICLE HISTORY
Received 14 October 2020
Accepted 27 December 2020

KEYWORDS
XPG; SNP; glioma; susceptibility; Chinese

Introduction

Glioma comprises approximately one-third of all brain tumour diagnoses in children, making them the most common central nervous system tumour arising in this group [1–4]. Although paediatric and adult glioma has a similar histology, high throughput gene sequencing and gene expression profile analysis points to differences [5–7]. As most studies on glioma focus on adults, searching for glioma susceptibility genes in children would help to identify high-risk individuals and develop prevention strategies.

Growing evidence from genome-wild association studies (GWASs) indicates that several genetic polymorphisms are implicated in glioma [8–10]. These include *TERT* rs2736100, *CCDC26* rs4295627, *CDKN2A-CDKN2B* rs4977756, *RTEL1* rs6010620, and *PHLDB1* rs498872, whilst the 9p21.3 locus is linked to this disease [11,12]. These studies suggest that genetic polymorphisms may affect the development of glioma.

DNA repair genes play a vital role in maintaining the genomic DNA stability and integrity, and thus affect tumour prognosis [13]. DNA repair genes participate in many crucial pathways including nucleotide excision repair (NER), which is responsible for removing a wide variety of DNA lesions, such as alkylating damage, bulky adducts, crosslinks, and oxidative DNA damage [14]. Thus far, at least eight complementation groups (XPA to G and ERCC1), which limit the rate of nucleotide excision repair mechanism, have been identified [15]. The *XPG* is one of eight key genes in the nucleotide excision repair pathway, single nucleotide polymorphisms (SNPs) having the potential to affect the development of cancer [16,17]. However, there is no literature reported regarding the associations between *XPG* SNPs and glioma. We therefore hypothesized links between five SNPs in *XPG* and the risk of childhood glioma.

Methods

We tested our hypothesis in a case/control study of 171 glioma cancer patients with a median (interquartile range) of 60 (24–96) months and 228 healthy

CONTACT L Zeng zlxx03@126.com Department of Pathology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou, Guangdong, 510623, China; ZJ Zhuo zhenjianzhuo@163.com Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou, Guangdong, 510623, China

[†]Li Yuan and Wan-Ming Hu contributed equally to this work.

controls enrolled between 2005 and 2019 from Guangzhou Women and Children's Medical Center and Sun Yat-sen University Cancer Center. The cases were all newly diagnosed and histopathologically confirmed as gliomas. All the healthy controls were selected from the same region as cases during the same period. Informed consent was obtained at the time of enrolment. This study was conducted under the approval of the Institutional Review Board of the participating hospitals.

The potentially functional SNPs were selected by using the NCBI dbSNP database and SNPinfo (http://snpinfo.nichs.nih.gov/snpinfo/snpfunc.htm) [18–20]. Specifically, the following items were set as the selection criteria: 1) located at the 5′ untranslated regions (UTR), upstream promoter region, coding region, and 3′ UTR of genes; 2) the minor allele frequency was >5% in Chinese Han populations; 3) no obvious linkage between paired SNPs in linkage disequilibrium (R^2 < 0.8). We also adopted SNPinfo (http://snpinfo.niehs.nih. gov/snpfunc.htm) to predict the potential functions of those polymorphisms; they could affect the activity of transcription factor binding sites or microRNA binding sites. We chose SNPs rs2094258 C > T, rs751402 C > T, rs2296147 T > C, rs1047768 T > C, rs873601 G > A in the *XPG* gene for analysis, as all of them met the listed criteria above. The genomic DNA kit (TianGen Biotech Co. Ltd., Beijing, China) was used for DNA extraction. Genomic DNA was extracted from blood samples donated from the participants using standard procedures. The concentration of DNA was determined using a NanoDrop ND-1000 Spectrophotometer. Genotyping was performed by Taqman real-time PCR using a 7900 Sequence Detection system (Thermo Fisher Scientific, Waltham, Mass, USA). The conditions of reactions were set as follows: pre-read stage at 60°C for 30 seconds, holding stage at 95°C 10 minutes, repeated 45 cycles each of denaturation at 95°C for 15 seconds, annealing and extension at 60°C for 1 minute. Ten per cent of the samples were randomly selected for repeated genotyping and the concordance was 100%.

The goodness-of-fit χ^2 test was performed to assess if the selected SNP deviated from Hardy–Weinberg equilibrium (HWE) among controls. The Mann–Whitney U test and the two-sided χ^2 test were used to compare demographic variables and genotype frequencies of cases and controls. To evaluate the strength of relationship between *XPG* SNPs and glioma susceptibility, odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed by unconditional logistic regression analyses with or without adjustment for age and gender. Expression quantitative trait loci (eQTL) analysis using GTEx portal website (http://www.gtexportal.org/home/) was adopted to explore the effects of SNPs on expression levels of nearby genes [21,22]. Only significant results were presented here for the eQTL analysis. The SAS statistical package (version 9.1; SAS institute, North Carolina, USA) was used to perform statistical analyses. All reported *P* values were two sided, and a $P < 0.05$ was considered statistically significant.

Results

The age of the 171 cases was 60 (24–96) months, and 87 (47.4%) were females. The age of the controls was 48 (25–73) months, of whom 93 (40.8%) were female (p = 0.269 and p = 0.190, respectively). Among these cases, 125 (73.1%) were astrocytic tumours, 24 (14.6%) were ependymoma, 14 (8.2%) were neuronal and mixed neuronal-glial tumours, and 7 (4.1%) were embryonal tumours. Furthermore, 103 (60.2%), 28 (16.4%), 15 (8.8%), and 25 (14.6%) were classified as WHO stages I, II, III, and IV, respectively.

As shown in Table 1, the observed genotype frequencies of the five SNPs are consistent with HWE in control subjects. Carrying the rs1047768 C allele and rs873601 A allele were associated with an increased risk of glioma whilst carrying the rs2094258 T allele had a protective effect. However, we failed to detect an association between the rs751402 C > T or rs2296147 T > C polymorphism and glioma risk, whether or not adjusted for age and sex. We further assessed the combined effect of risk genotypes. Subjects carrying 5 risk genotypes had a significantly increased glioma risk when compared with those carrying 0–4 risk genotypes.

To evaluate the effects of selected *XPG* polymorphisms on glioma risk among different subgroups, stratified analysis was conducted based on the age, gender, subtypes, and clinical stages (Table 2). Compared to the rs2094258 CC/CT genotype, the protective effect of TT genotypes was more predominant for males and astrocytic tumours. Interestingly, we detected that subjects with rs1047768 CT/CC genotype were associated with an elevated glioma risk among males, astrocytic tumours and those with clinical stage I+ II compared with the reference group. Similarly, when compared with GG genotype, carriers of rs873601 AG/AA genotypes had a significantly increased risk of glioma among males, ependymoma, and those with clinical stage I+ II.

To assess the cumulative effects of protective genotypes among subgroups, we further performed a combined analysis. Results show that subjects harbouring 5 risk genotypes had a significantly increased glioma risk in the following subgroups: age >60 months, males, subtype of astrocytic tumours, and low-grade clinical stage.

To further assess whether the functional relevance of rs2094258 affects mRNA expression, we analysed eQTL of genes surrounding rs2094258 using released data from GTEx. It showed that individuals carrying the rs2094258 T genotype had significantly higher

Table 1. Association between *XPG* polymorphisms and glioma susceptibility.

Genotype	Cases (N = 171)	Controls (N = 228)	*P* [a]	Adjusted OR (95% CI) [b]	*P* [b]
rs2094258 C > T (HWE = 0.969)					
CC	79 (46.20)	94 (41.23)		1.00	
CT	82 (47.95)	105 (46.05)		0.90 (0.59–1.37)	0.626
TT	10 (5.85)	29 (12.72)		0.38 (0.17–0.83)	0.016
Additive			0.071	0.72 (0.53–0.99)	0.045
Dominant	92 (53.80)	134 (58.77)	0.321	0.79 (0.52–1.18)	0.243
Recessive	161 (94.15)	199 (87.28)	0.022	0.40 (0.19–0.85)	0.017
rs751402 C > T (HWE = 0.238)					
CC	58 (33.92)	86 (37.72)		1.00	
CT	89 (52.05)	101 (44.30)		1.28 (0.82–2.00)	0.279
TT	24 (14.04)	41 (17.98)		0.90 (0.49–1.66)	0.737
Additive			0.984	1.01 (0.75–1.34)	0.966
Dominant	113 (66.08)	142 (62.28)	0.434	1.17 (0.77–1.78)	0.463
Recessive	147 (85.96)	187 (82.02)	0.291	0.78 (0.45–1.36)	0.385
rs2296147 T > C (HWE = 0.545)					
TT	99 (57.89)	143 (62.72)		1.00	
CT	63 (36.84)	77 (33.77)		1.26 (0.82–1.94)	0.287
CC	9 (5.26)	8 (3.51)		1.59 (0.59–4.31)	0.362
Additive			0.259	1.26 (0.89–1.79)	0.191
Dominant	72 (42.11)	85 (37.28)	0.329	1.30 (0.86–1.96)	0.218
Recessive	162 (94.74)	220 (96.49)	0.391	1.47 (0.55–3.92)	0.447
rs1047768 T > C (HWE = 0.939)					
TT	83 (48.54)	133 (58.33)		1.00	
CT	77 (45.03)	82 (35.96)		1.59 (1.04–2.43)	0.032
CC	11 (6.43)	13 (5.70)		1.34 (0.57–3.17)	0.502
Additive			0.088	1.36 (0.98–1.90)	0.068
Dominant	88 (51.46)	95 (41.67)	0.052	1.56 (1.04–2.33)	0.033
Recessive	160 (93.57)	215 (94.30)	0.761	1.11 (0.48–2.56)	0.813
rs873601 G > A (HWE = 0.382)					
GG	31 (18.13)	62 (27.19)		1.00	
AG	94 (54.97)	120 (52.63)		1.57 (0.94–2.64)	0.085
AA	46 (26.90)	46 (20.18)		2.04 (1.11–3.72)	0.021
Additive			0.022	1.42 (1.05–1.92)	0.022
Dominant	140 (81.87)	166 (72.81)	0.034	1.70 (1.04–2.79)	0.035
Recessive	125 (73.10)	182 (79.82)	0.115	1.47 (0.92–2.37)	0.109
Combined effect of risk genotypes[c]					
0–4	109 (63.74)	175 (76.75)		1.00	
5	62 (36.26)	53 (23.25)	0.005	1.97 (1.26–3.08)	0.003

OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium. [a] χ^2 test for genotype distributions between glioma patients and cancer-free controls. [b] Adjusted for age and gender. [c] Risk genotypes were carriers with rs2094258 CC/CT, rs751402 CC/CT, rs2296147 CT/CC, rs1047768 CT/CC, rs873601 AG/AA genotypes.A pair of alleles such as A/G, if A is a less frequent gene, then Dominant model (GA+AA vs GG), Recessive model (AA vs GA +GG), Additive model (AA vs GA vs GG).

METTL21EP mRNA level (coding a methyltransferase) in the brain-cerebellum (Figure 1A) and brain-caudate (basal ganglia) (Figure 1B). However, rs2094258 T allele was significantly associated with lower expression levels of *BIVM* level (whose product is not fully characterized) in the whole blood (Figure 1C).

Discussion

Screening SNPs loci of DNA repair genes and exploring the biological significance helps to provide potential opportunities to individualize therapy. We genotyped five SNPs in *XPG* (located at 13q33) involved in the NER pathway and assessed their associations with glioma risk. The main role of XPG protein is to act as an endonuclease to remove DNA damage fragments from the 3′ end and plays a crucial role in maintaining the stability of DNA structure [23]. As the core gene of DNA repair gene, *XPG* can increase the DNA repair activity, and tumour cells with higher DNA repair ability are more likely to metastasize and invade [24].

To date, many SNPs in *XPG* have been identified, rs2094258 C > T, rs751402 C > T, rs2296147 T > C, rs1047768 T > C, rs873601 G > A being the most frequently studied. SNP rs2094258 C > T is located in the intron region of the *XPG* and participates in the initiation of transcriptional-coupled DNA repair, to modulate gene transcription and protein translation [25]. Wang et al. showed that rs2094258 is not associated with the long-term survival of colorectal cancer cases [26]. Zhang et al. conducted a meta-analysis indicated that *XPG* rs2094258 SNP is associated with an increased risk of gastric cancer [27]. rs751402 C > T is located in the E2F1/YY1 binding sites in the proximal promoter of *XPG*, and this SNP may reduce the DNA repair ability of XPG by changing the affinity of transcription factors [28]. A meta-analysis found that rs751402 C > T is significantly associated with the overall risk of several cancers, patients with TT genotype had an increase cancer-associated risk by 18% compare to CC genotype [29]. Similarly, a meta-analysis of *XPG* and tumour susceptibility demonstrated the same

Table 2. Stratification analysis of risk genotypes with glioma susceptibility.

Variables	rs2094258 (cases/controls)				rs1047768 (cases/controls)				rs873601 (cases/controls)				Risk genotypes (cases/controls)			
	CC/CT	TT	AOR (95% CI) [a]	*P* [a]	TT	CT/CC	AOR (95% CI) [a]	*P* [a]	GG	AG/AA	AOR (95% CI) [a]	*P* [a]	0–4	5	AOR (95% CI) [a]	*P* [a]
Age (month)																
<60	80/106	5/13	0.50 (0.17–1.47)	0.210	37/64	48/55	1.51 (0.86–2.65)	0.150	17/36	68/83	1.78 (0.92–3.47)	0.088	52/86	33/33	1.67 (0.92–3.02)	0.092
≥60	81/93	5/16	0.35 (0.12–1.00)	0.050	46/69	40/40	1.48 (0.83–2.64)	0.184	14/26	72/83	1.67 (0.81–3.47)	0.166	57/89	29/20	2.20 (1.14–4.27)	0.020
Gender																
Females	73/82	8/11	0.75 (0.28–2.01)	0.571	42/50	39/43	1.15 (0.63–2.11)	0.652	21/27	60/66	1.09 (0.55–2.16)	0.797	54/68	27/25	1.38 (0.71–2.67)	0.346
Males	88/117	2/18	0.15 (0.03–0.65)	0.011	41/83	49/52	1.98 (1.15–3.43)	0.014	10/35	80/100	2.79 (1.30–5.99)	0.009	55/107	35/28	2.63 (1.43–4.83)	0.002
Subtypes																
Astrocytic tumours	118/199	7/29	0.39 (0.16–0.93)	0.033	59/133	66/95	1.65 (1.05–2.60)	0.030	23/62	102/166	1.61 (0.93–2.80)	0.090	77/175	48/53	2.19 (1.34–3.57)	0.002
Ependymoma	123/199	2/29	0.65 (0.14–2.93)	0.574	13/133	12/95	1.16 (0.50–2.70)	0.732	2/62	23/166	4.84 (1.10–21.34)	0.037	17/175	8/53	1.40 (0.56–3.49)	0.468
Neuronal and mixed	14/199	0/29	/	/	6/133	8/95	1.86 (0.62–5.63)	0.272	2/62	12/166	2.35 (0.51–10.91)	0.275	8/175	6/53	2.49 (0.81–7.66)	0.112
Embryonal tumours	6/199	1/29	0.75 (0.06–8.78)	0.817	5/133	2/95	0.48 (0.08–2.98)	0.432	4/62	3/166	0.16 (0.03–1.00)	0.050	7/175	0/53	/	/
Clinical stage																
I+ II	122/199	9/29	0.49 (0.22–1.07)	0.073	60/133	71/95	1.70 (1.10–2.64)	0.017	22/62	109/166	1.84 (1.06–3.19)	0.030	79/175	52/53	2.23 (1.39–3.57)	0.001
III+IV	39/199	1/29	0.15 (0.02–1.19)	0.073	23/133	17/95	1.09 (0.55–2.19)	0.801	9/62	31/166	1.22 (0.54–2.76)	0.629	30/175	10/53	1.16 (0.52–2.58)	0.717

OR, odds ratio; CI, confidence interval. [a] Adjusted for age and gender, omitting the corresponding stratify factor.

results, rs751402 C > T increasing cancer susceptibility in dominant, additive, and recessive modes [30]. rs2296147 T > C is located in the 5′ untranslated region of *XPG*, proposed as a transcription factor binding site for p53 [31]. Most results showed that there was no link between rs2296147 and most types of tumour [19]. Another study found that patients carrying the rs2296147 CT/TT genotype had a significantly shorter median 10 years progression-free survival than those carrying CC genotype, indicating that *XPG* rs2296147 CT/TT variants confer a significant survival disadvantage in patients with colorectal cancer [26]. These results may be related to regional differences, small sample size, or heterogeneity of clinical characteristics. rs1047768T>C is a synonymous non-shear mutation of His46His located on exon region of *XPG*, and its relationship with cancer may be generated through the specificity of enzymes, which promoting substance-specific transformation [32]. Several studies have linked rs1047768 to breast cancer, lung cancer and gastric cancer [33]. rs873601 G > A is located in miRNA binding sites and alters XPG expression by regulating miRNA–mRNA interaction [18]. rs873601 has been significantly linked with the overall cancer risk, the gastric risk being 18% higher for patients with AA genotype compared to patients with GC genotype [30]. He et al. found that the genotype variation of *XPG* rs873601AA was associated with a high risk of gastric cancer through the analysis of 1,125 gastric cancer cases and 1,196 cancer-free controls, and the allele mutation of *XPG* rs873601AA would decrease *XPG* mRNA in gastric cancer tissues [18]. However, the rs873601 G > A SNP was not associated with susceptibility to gastric cardia adenocarcinoma [34]. The discrepancies among studies may be due to tumour specificity, ethnic, and demographic differences. eQTL evidence suggested that the T allele in rs2094258 is significantly associated with increased *METTL21EP* mRNA level in the brain-cerebellum and brain-caudate (basal ganglia). However, rs2094258 T allele was significantly associated with lower expression levels of *BIVM* level in the whole blood. This conclusion requires further interpretation as the roles of *METTL21EP* and *BIVM* remain to be revealed. In all, more functional experiments are needed to support this possible mechanism.

Here, we assess the relationship between *XPG* polymorphism and glioma risk. our analysis indicates that rs2094256 C > T polymorphism had a protective effect against developing glioma, but rs1047768 T > C and rs873601 G > A polymorphisms associated with higher glioma risk. Variants at a single locus may contribute limitedly to risk of cancer due to their weak penetrance. Anyway, subjects carrying 5 risk genotypes had a significantly increased glioma risk when compared with those carrying 0–4 risk genotype. The current study has some limitations. This study only examined five functional SNPs, further

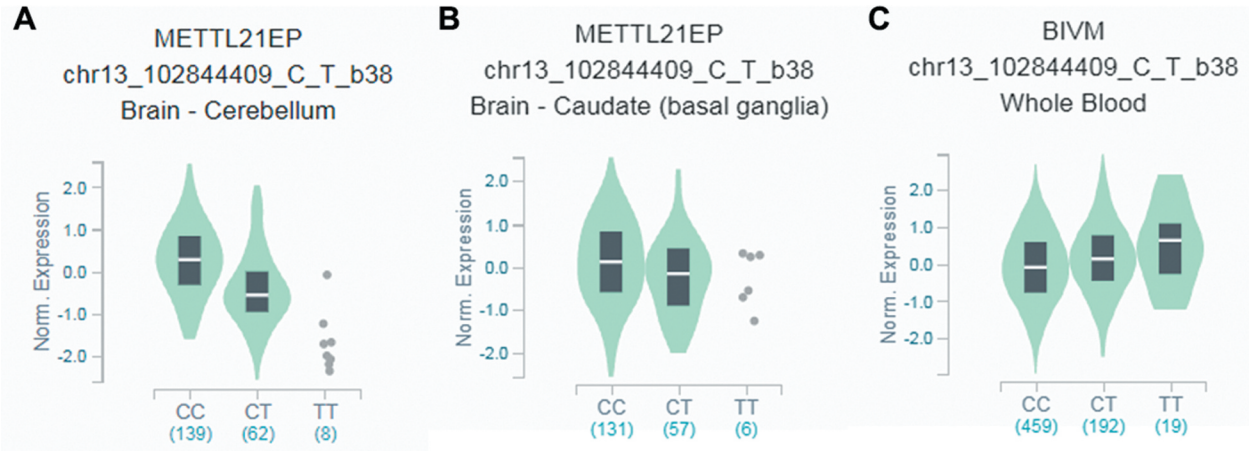

Figure 1. Functional relevance of rs2094258 on neighbouring genes expression in GTEx database. rs2094258 T genotype had significantly higher *METTL21EP* mRNA level in the (A) brain-cerebellum and (B) brain-caudate (basal ganglia), but significantly lower *BIVM* level in the (C) whole blood. Note: The thick black lines in the middle represent the range of quartile, the white lines represent median of the information, the width of green parts represent the frequency.

studies containing more potentially functional SNPs in the *XPG* gene that might play a key role in glioma development are needed. And our work lacks *in vitro* data to support a role for these polymorphisms in glioma, which should be explored in the future. Third, we could not assess the environmental effects on glioma risk. Thus, it is debatable whether the observed impact of the *XPG* SNPs is modified by these factors. Fourth, the sample size of cases was still modest, and more samples needed to be included in the future. Of note, caution should be taken when interpreting the stratification analysis due to the small sample size. Finally, this study was a hospital-based case–control study with subjected from South China, the current findings may not well represent other races and ethnicities.

This study represents an advance in biomedical science because it shows that certain SNPs in *XPG* are linked to the risk of glioma and vary with sex, type of tumour and clinical stage of the disease, and so warrant additional studies.

Summary table

What is known about this subject:
- *XPG* codes a protein with important roles in the repair of damaged DNA.
- Loss of function mutations in *XPG* is linked to dermal pathology and to colorectal and gastric carcinoma

What this paper adds:
- *XPG* SNP rs2094258 C > T is associated with a decreased glioma risk
- *XPG* SNPs rs1047768 C or rs873601 A allele are linked to increased glioma risk
- *XPG* SNP rs2094258 is linked with the expression of its surrounding genes

Disclosure statement

The authors declare no conflicts of interest.

Funding

This study was supported by Guangzhou Science, Technology and Innovation Commission [201804010042]; National Natural Science Foundation of China [81802346]; National Natural Science Foundation of China [81672496]; Natural Science Foundation of Guangdong Province [2020A1515010188]; Postdoctoral Research Foundation of China [2020T130132].

ORCID

ZJ Zhuo http://orcid.org/0000-0003-0142-4086

Ethical approval

This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center.

References

[1] Pak-Yin Liu A, Moreira DC, Sun C, et al. Challenges and opportunities for managing pediatric central nervous system tumors in China. Pediatr Investig. 2020;4:211–217.
[2] Jones DTW, Kieran MW, Bouffet E, et al. Pediatric low-grade gliomas: next biologically driven steps. Neuro Oncol. 2018;20:160–173.
[3] Weller M, Wick W, Aldape K, et al. Glioma. Nat Rev Dis Primers. 2015;1:15017.
[4] Cordier D, Gerber M, Brand S. Effects of two types of exercise training on psychological well-being, sleep, quality of life and physical fitness in patients with high-grade glioma (who iii and iv): study protocol for a randomized controlled trial. Cancer Commun (Lond). 2019;39:46.
[5] Davis ME. Epidemiology and overview of gliomas. Semin Oncol Nurs. 2018;34:420–429.
[6] Broniscer A, Baker SJ, West AN, et al. Clinical and molecular characteristics of malignant transformation of low-grade glioma in children. J Clin Oncol. 2007;25:682–689.

[7] Terashima K, Chow K, Jones J, et al. Long-term outcome of centrally located low-grade glioma in children. Cancer. 2013;119:2630–2638.
[8] Kinnersley B, Labussiere M, Holroyd A, et al. Genome-wide association study identifies multiple susceptibility loci for glioma. Nat Commun. 2015;6:8559.
[9] Melin BS, Barnholtz-Sloan JS, Wrensch MR, et al. Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nat Genet. 2017;49:789–794.
[10] Wrensch M, Jenkins RB, Chang JS, et al. Variants in the cdkn2b and rtel1 regions are associated with high-grade glioma susceptibility. Nat Genet. 2009;41:905–908.
[11] Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. Nat Genet. 2009;41:899–904.
[12] Dahlin AM, Wibom C, Andersson U, et al. Genetic variants in the 9p21.3 locus associated with glioma risk in children, adolescents, and young adults: A case-control study. Cancer Epidemiol Biomarkers Prev. 2019;28:1252–1258.
[13] Rajaraman P, Hutchinson A, Wichner S, et al. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. Neuro Oncol. 2010;12:37–48.
[14] Chitale S, Richly H. Timing of DNA lesion recognition: ubiquitin signaling in the NER pathway. Cell Cycle. 2017;16:163–171.
[15] Lans H, Hoeijmakers JHJ, Vermeulen W, et al. The DNA damage response to transcription stress. Nat Rev Mol Cell Biol. 2019;20:766–784.
[16] Mlak R, Krawczyk P, Homa-Mlak I, et al. Predictive value of single nucleotide polymorphisms of ERCC1, XPA, XPC, XPD and XPG genes, involved in NER mechanism in patients with advanced NSCLC treated with cisplatin and gemcitabine. Pathol Oncol Res. 2019;25:1035–1045.
[17] Ibarrola-Villava M, Pena-Chilet M, Fernandez LP, et al. Genetic polymorphisms in DNA repair and oxidative stress pathways associated with malignant melanoma susceptibility. Eur J Cancer. 2011;47:2618–2625.
[18] He J, Qiu LX, Wang MY, et al. Polymorphisms in the XPG gene and risk of gastric cancer in Chinese populations. Hum Genet. 2012;131:1235–1244.
[19] Hua RX, Zhuo ZJ, Zhu J, et al. XPG gene polymorphisms contribute to colorectal cancer susceptibility: A two-stage case-control study. J Cancer. 2016;7:1731–1739.
[20] Zhuo ZJ, Liu W, Zhang J, et al. Functional polymorphisms at ERCC1/XPF genes confer neuroblastoma risk in Chinese children. EBioMedicine. 2018;30:113–119.
[21] Consortium GT. Human genomics. The genotype-tissue expression (GTEX) pilot analysis: multitissue gene regulation in humans. Science. 2015;348:648–660.
[22] Zhuo Z, Zhou C, Fang Y, et al. Correlation between the genetic variants of base excision repair (ber) pathway genes and neuroblastoma susceptibility in eastern Chinese children. Cancer Commun (Lond). 2020;40:641–646.
[23] Dunand-Sauthier I, Hohl M, Thorel F, et al. The spacer region of xpg mediates recruitment to nucleotide excision repair complexes and determines substrate specificity. J Biol Chem. 2005;280:7030–7037.
[24] Tsutakawa SE, Sarker AH, Ng C, et al. Human xpg nuclease structure, assembly, and activities with insights for neurodegeneration and cancer from pathogenic mutations. Proc Natl Acad Sci U S A. 2020;117:14127–14138.
[25] Chen YZ, Guo F, Sun HW, et al. Association between xpg polymorphisms and stomach cancer susceptibility in a Chinese population. J Cell Mol Med. 2016;20:903–908.
[26] Wang F, Zhang SD, Xu HM, et al. Xpg rs2296147 t>c polymorphism predicted clinical outcome in colorectal cancer. Oncotarget. 2016;7:11724–11732.
[27] Zhang Z, Yin J, Xu Q, et al. Association between the xpg gene rs2094258 polymorphism and risk of gastric cancer. J Clin Lab Anal. 2018;32:e22564.
[28] Crawford EL, Blomquist T, Mullins DN, et al. Cebpg regulates ERCC5/XPG expression in human bronchial epithelial cells and this regulation is modified by E2F1/YY1 interactions. Carcinogenesis. 2007;28:2552–2559.
[29] Huang J, Liu X, Tang LL, et al. Xpg gene polymorphisms and cancer susceptibility: evidence from 47 studies. Oncotarget. 2017;8:37263–37277.
[30] Han C, Huang X, Hua R, et al. The association between XPG polymorphisms and cancer susceptibility: evidence from observational studies. Medicine (Baltimore). 2017;96:e7467.
[31] Mohrenweiser H. Survey of polymorphic sequence variation in the immediate 5′ region of human DNA repair genes. Mutat Res. 2007;616:221–226.
[32] Wang H, Liu J, Zhang R, et al. The relationship between DNA repair genes (XPA, XPF, XPG) polymorphism and the risk of preeclampsia in Chinese Han women. Pregnancy Hypertens. 2018;14:145–149.
[33] Hussain SK, Mu LN, Cai L, et al. Genetic variation in immune regulation and DNA repair pathways and stomach cancer in China. Cancer Epidemiol Biomarkers Prev. 2009;18:2304–2309.
[34] Zhou RM, Niu CX, Wang N, et al. XPG gene polymorphisms and the risk of gastric cardia adenocarcinoma. Genet Test Mol Biomarkers. 2016;20:432–437.