Pharmacogenomics and Personalized Medicine

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ORIGINAL RESEARCH

No Association Between *FTO* Gene Polymorphisms and Central Nervous System Tumor Susceptibility in Chinese Children

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine

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Background: Central nervous system (CNS) tumor is a malignancy commonly seen occurring in childhood, worldwide. Fat mass and obesity-associated (FTO) enzyme, initially identified as an obesity-related protein, also functions as a susceptibility gene for cancers. However, predisposing effect of *FTO* gene single nucleotide polymorphisms (SNPs) on CNS tumor risk remains unknown.

Methods: Herein, we genotyped 314 CNS tumor patients and 380 healthy controls samples from three hospitals to explore whether *FTO* gene SNPs impact CNS tumor risk. TaqMan SNP genotyping assay was applied for the genotyping. Odds ratios (ORs) and 95% confidence intervals (CIs), generated from multinomial logistic regression, were applied to determine the associations of SNPs (rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, and rs8047395 A>G) in *FTO* gene with risk of CNS tumor.

Results: We failed to detect significant associations between *FTO* gene SNPs and CNS tumor risk, either in single-locus or combined analysis. A significantly increased ependymoma risk was found for carriers with 3–4 risk genotypes in comparison to 0–2 risk genotypes (adjusted OR=1.94, 95% CI=1.11–3.37, *P*=0.020).

Conclusion: Our data indicated that *FTO* gene SNPs are unlikely to have large effects on CNS tumor risk but may have weaker effects.

Keywords: CNS tumor, risk, *FTO*, polymorphism, Chinese

Introduction

Central nervous system (CNS) tumors comprise about 20% of all malignancies occurring in childhood and adolescence.[1] Gliomas account for the largest proportion of malignant brain tumors at 80%.[2,3] Gliomas are heterogeneous primary brain tumors that originate from neuroglial stem or progenitor cells.[4,5] Pediatric low-grade gliomas (LGGs), or WHO grade I or II gliomas, account for about 30% of all childhood CNS tumors. These subtype tumors rarely undergo malignant transformation with a favorable prognosis. However, for WHO grade III or IV high-grade gliomas (HGGs),[6] the prognosis is poor at only 20% for 5-year survival rate.[7] Of note, the development of new therapies such as immune therapies and target therapies has helped to improve the survival of CNS tumor patients.[8]

Exposure to high dose ionizing radiation is the most firmly established environmental risk factor for CNS tumor.[9–11] Other factors such as cellular phones, tobacco uses, and allergies/atopic disease have been extensively investigated for CNS tumor risk.[12,13] However, such relationships remain inconclusive. Heritable genetic

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http://doi.org/10.2147/PGPM.S289345

variants are important factors associated with CNS tumor risk. Several genome-wide association studies of glioma patients have identified SNPs in *RTEL1, PHLDB1, CCDC26, TP53, EGFR*, and *CDKN2B* genes as CNS tumor risk-associated susceptibility polymorphisms.[14–17] Candidate gene studies focusing on genes thought to be involved in gliomagenesis also identified multiple genetic variants associated with risk of CNS tumor.[18,19] All the genetic variants identified so far only reveal a piece of the genetic landscape of CNS tumor.

The fat mass and obesity-associated (*FTO*) gene was originally identified as an obesity susceptibility gene by genome-wide association studies (GWASs).[20] Multiple single-nucleotide polymorphisms (SNPs) located in the intron 1 of *FTO* gene have been well recognized for their strong relationships with the risk of obesity.[21–24] The contribution of *FTO* gene SNPs to cancer risk also has been demonstrated previously.[25] For example, Kaklamani et al found that intron 1 (obesity-associated region) SNPs rs7206790, rs8047395, rs9939609, and rs1477196 in *FTO* gene were tightly associated with risk of breast cancer. It is highly possible that the obesity-associated SNPs could cause an increased risk to overweight and obese patients and lead to an increased cancer susceptibility.[26] Notably, SNPs outside of intron 1 of *FTO* gene were also found to impact the susceptibility of cancer.[27] Indeed, *FTO* has been reported as an oncogenic gene in various cancers. Of note, *FTO* was the first identified N6-methyladenosine (m^6A) demethylase of eukaryotic mRNA.[28] The aberrant m^6A modifications mediated by *FTO* expression contributed to the development of cancers.[29–31] m^6A RNA methylation regulators are crucial participants in the malignant progression of CNS tumor. *FTO* may preferentially mediate demethylation of different methylation targets in CNS tumor.[32] The strong relation between *FTO* gene as well as its SNPs and cancer motivated us to evaluate the association of *FTO* gene SNPs with CNS tumor risk. This study represents the first attempt to explore *FTO* gene SNPs in relation to CNS tumor risk in a Chinese population.

Materials and Methods

Study Subjects

In total, three hospitals located in Wenzhou, Guangzhou, and Changsha, participated in this project. All patients were histopathologically confirmed with CNS tumor without previous radiotherapy or chemotherapy, while cancer-free controls were enrolled from hospital visitors in the same hospital during the same period. The detailed criteria for diagnosing CNS tumor was based on the 2016 World Health Organization classification of tumors of the CNS.[6] Controls were frequency-matched to the cases by age and gender. Controls with other tumors, neurological disease, congenital genetic disease, and infectious disease were excluded. None of the study subjects had a blood relationship. Written informed consent was provided from all enrolled patients' guardians prior to study commencement. The research protocol for this study was reviewed and approved by the Institutional Review Boards of the participating hospitals (Xiangya Hospital, Guangzhou Women and Children's Medical Center, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University). This study was conducted in accordance with the Declaration of Helsinki.

Genotyping

Potentially functional polymorphisms in *FTO* gene were screened from the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP) and SNPinfo (http://snpinfo.niehs.nih.gov/snpfunc.htm). Detailed information on SNP selection and genotyping could be found previously.[33–35] Four SNPs rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, and rs8047395 A>G in *FTO* gene were screened out for analysis. Genomic DNA extraction from blood samples was accomplished through QIAamp DNA blood mini kit (QIAGEN Inc., Valencia, CA, USA). The DNA extraction process was carried out in accordance with the manufacturer's instructions. To ensure genotyping accuracy, a blinded fashion was adopted without knowing the case-control status of the subject. Primers and fluorescently labeled probes were purchased from Applied Biosystems for detection of both the wild-type and variant alleles. Genotyping of SNPs was performed with a TaqMan SNP Genotyping Assay (Applied Biosystems, USA), with details in a previous study.[33] The conditions of reactions were set as follow: preread stage at 60°C for 30 seconds, holding stage at 95°C for 10 minutes, repeated 45 cycles each of denaturation at 95°C for 15 seconds, annealing and extension at 60°C for 1 minute. For quality control purpose, we also randomly selected 10% control samples to run a second genotype. A 100% rate was achieved for the second run data compared to the original data.

Statistical Analysis

Differences between case and control groups clinical variables were evaluated using Chi-square test or *t*-test, as appropriate. A goodness-of-fit χ^2 test was applied to test whether the expected genotypes with the observed ones were in Hardy–Weinberg equilibrium (HWE) in the controls. The calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs) were under multivariate logistic regression adjusted by sex and age, and further applied to determine the association between each SNP and CNS tumor risk. The $P<0.05$ indicated statistical significance. Statistical analysis was performed with SAS v10.0 (SAS Institute Inc., Cary, NC, USA).

Results

Population Characteristics

Frequency distributions of age ($P=0.461$) and gender ($P=0.379$) were similar between 314 patients and 380 controls, indicating adequate matching on these factors. The mean age for cases was 70.46 ± 48.39 months and for controls 64.19 ± 37.38 months. Cases were categorized as astrocytic tumors (214, 68.15%), ependymoma (61, 19.43%), neuronal and mixed neuronal-glial tumors (25, 7.96%), embryonal tumors (12, 3.82%), and not available (NA) (2, 0.64%). As to WHO stages, 151 (48.09%) CNS tumor cases were classified into stage I, 73 (23.23%) into stage II, 36 (11.46%) into stage III, 53 (16.88%) into stage IV, and 1 (0.32%) into NA (Table 1).

Effect of *FTO* Gene SNPs on CNS Tumor Risk

The SNPs of *FTO* gene and their relationships with CNS tumor risk are summarized in Table 2. As expected, all the four SNPs rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, and rs8047395 A>G in *FTO* gene were in Hardy–Weinberg equilibrium (HWE), each with a value of 0.538, 0.835, 0.856, and 0.851, respectively. For the four single locus analysis, none of them could significantly predispose to CNS tumor risk, respectively. We then treated rs1477196 GG/GA, rs9939609 TA/AA, rs7206790 CG/GG, rs8047395 AA/AG genotypes as risk genotypes. Subjects with 1, 2, 3, and 4 risk genotypes still could not impact risk of CNS tumor. Similar negative results were obtained for 3–4 risk genotypes in comparison to 0–2 risk genotypes.

Table 1 Frequency Distribution of Selected Variables in CNS Tumor Patients and Cancer-Free Controls in Combined Subjects

Variables	Cases (N=314)		Controls (N=380)		P^a
	No.	**%**	**No.**	**%**	
Age range, month	1.00–168.00		1.00–168.00		0.461
Mean ± SD	70.46 ± 48.39		64.19 ± 37.38		
<60	135	42.99	174	45.79	
≥60	179	57.01	206	54.21	
Sex					0.379
Female	146	46.50	164	43.16	
Male	168	53.50	216	56.84	
Subtypes					
Astrocytic tumors	214	68.15	/	/	
Ependymoma	61	19.43	/	/	
Neuronal and mixed neuronal-glial tumours	25	7.96	/	/	
Embryonal tumors	12	3.82	/	/	
NA	2	0.64	/	/	
WHO stages					
I	151	48.09	/	/	
II	73	23.23	/	/	
III	36	11.46	/	/	
IV	53	16.88	/	/	
NA	1	0.32	/	/	

Note: [a]Two-sided χ^2 test for distributions between CNS tumor patients and cancer-free controls.

Abbreviations: CNS, central nervous sytesm; SD, standard deviation; NA, not available.

Stratification Analysis

The relationships between SNP rs7206790, risk genotypes and CNS tumor risk, respectively, were further determined by stratified analyses in age, gender, subtypes, and clinical stages subgroups (Table 3). Compared to CC genotype, rs7206790 CG/GG could not modify risk of CNS tumor, under any subgroup. Compared to 0–2 risk genotypes, carriers with 3–4 risk genotypes were more likely to develop ependymoma (adjusted OR=1.94, 95% CI=1.11–3.37, $P=0.020$).

Discussion

Our study represents the first candidate gene-based association study to assess the relationship between *FTO* gene SNPs and CNS tumor risk in a Chinese population in three multicenter case-control studies. In general, no associations with risk of CNS tumor reached statistical significance in either individual or combined SNPs. We did observe that individuals with 3–4 risk genotypes were significantly associated with increased risk of CNS tumor.

Table 2 Association Between *FTO* Gene Polymorphisms and CNS Tumor Susceptibility in Chinese Children

Genotype	Cases (N=314)	Controls (N=380)	P^a	Crude OR (95% CI)	P	Adjusted OR (95% CI)^b	P^b
rs1477196 G>A (HWE=0.538)							
GG	178 (56.69)	216 (56.84)		1.00		1.00	
GA	117 (37.26)	138 (36.32)		1.03 (0.75–1.41)	0.860	1.00 (0.73–1.37)	0.984
AA	19 (6.05)	26 (6.84)		0.89 (0.48–1.66)	0.706	0.89 (0.47–1.66)	0.707
Additive			0.892	0.98 (0.77–1.25)	0.892	0.97 (0.76–1.24)	0.795
Dominant	136 (43.31)	164 (43.16)	0.967	1.01 (0.74–1.36)	0.967	0.98 (0.72–1.33)	0.893
Recessive	295 (93.95)	354 (93.16)	0.674	0.88 (0.48–1.62)	0.674	0.89 (0.48–1.64)	0.704
rs9939609 T>A (HWE=0.835)							
TT	236 (75.16)	294 (77.37)		1.00		1.00	
TA	68 (21.66)	80 (21.05)		1.06 (0.73–1.53)	0.759	1.08 (0.74–1.55)	0.701
AA	10 (3.18)	6 (1.58)		2.08 (0.74–5.80)	0.163	2.11 (0.75–5.93)	0.156
Additive			0.306	1.17 (0.86–1.59)	0.306	1.19 (0.87–1.61)	0.272
Dominant	78 (24.84)	86 (22.63)	0.495	1.13 (0.80–1.61)	0.495	1.15 (0.81–1.63)	0.446
Recessive	304 (96.82)	374 (98.42)	0.161	2.05 (0.74–5.71)	0.169	2.08 (0.74–5.82)	0.163
rs7206790 C>G (HWE=0.856)							
CC	214 (68.15)	275 (72.37)		1.00		1.00	
CG	88 (28.03)	96 (25.26)		1.18 (0.84–1.66)	0.345	1.20 (0.85–1.68)	0.304
GG	12 (3.82)	9 (2.37)		1.71 (0.71–4.14)	0.232	1.71 (0.70–4.14)	0.239
Additive			0.161	1.22 (0.92–1.62)	0.161	1.23 (0.93–1.64)	0.145
Dominant	110 (31.85)	105 (27.63)	0.226	1.22 (0.88–1.70)	0.226	1.24 (0.89–1.72)	0.199
Recessive	302 (96.18)	371 (97.63)	0.266	1.64 (0.68–3.94)	0.270	1.62 (0.67–3.93)	0.282
rs8047395 A>G (HWE=0.851)							
AA	124 (39.49)	142 (37.37)		1.00		1.00	
AG	151 (48.09)	182 (47.89)		0.95 (0.69–1.31)	0.756	0.94 (0.68–1.30)	0.693
GG	39 (12.42)	56 (14.74)		0.80 (0.50–1.28)	0.350	0.79 (0.49–1.27)	0.331
Additive			0.391	0.91 (0.73–1.13)	0.391	0.90 (0.72–1.13)	0.357
Dominant	190 (60.51)	238 (62.63)	0.567	0.91 (0.67–1.24)	0.567	0.90 (0.66–1.23)	0.513
Recessive	275 (87.58)	324 (85.26)	0.377	0.82 (0.53–1.27)	0.377	0.82 (0.53–1.27)	0.374
Combined effect of risk genotypes^c							
0	17 (5.41)	25 (6.58)	0.228	1.00		1.00	
1	21 (6.69)	30 (7.89)		1.03 (0.45–2.36)	0.946	1.02 (0.44–2.34)	0.972
2	158 (50.32)	197 (51.84)		1.18 (0.62–2.26)	0.619	1.16 (0.61–2.24)	0.649
3	61 (19.43)	67 (17.63)		1.34 (0.66–2.72)	0.419	1.37 (0.67–2.78)	0.389
4	57 (18.15)	61 (16.05)		1.37 (0.67–2.81)	0.383	1.37 (0.67–2.80)	0.390
0–2	196 (62.42)	252 (66.32)		1.00		1.00	
3–4	118 (37.58)	128 (33.68)	0.286	1.19 (0.87–1.62)	0.286	1.21 (0.88–1.66)	0.233

Notes: $^a\chi^2$ test for genotype distributions between CNS tumor patients and cancer-free controls. ^{b}Adjusted for age and sex. ^{c}Risk genotypes were carriers with rs1477196 GG/GA, rs9939609 TA/AA, rs7206790 CG/GG, rs8047395 AA/AG genotypes.

Abbreviations: CNS, central nervous system; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

FTO has been well documented to be involved in various types of cancers, such as acute myeloid leukemias (AMLs),[36] breast cancer,[37] and ovarian cancer.[38] More recently, evidence regarding role of FTO on CNS tumor are also emerging. Cui et al[39] demonstrated that inhibition of the RNA demethylase FTO could intensively suppress the development of glioblastoma stem (-like) cells (GSCs). Inhibition of FTO could enhances the anti-glioma effect of temozolomide by targeting MYC-miR-155/23a cluster-MXI1 feedback circuit.[40] Tao et al[41] found that protein level of FTO was significantly lower in gliomas than that in normal tissues. Further mechanism experiment revealed

Table 3 Stratification Analysis of Risk Genotypes with CNS Tumor Susceptibility

Variables	**rs7206790**		**AOR (95% CI)**[a]	***P***[a]	**Risk Genotypes**		**AOR (95% CI)**[a]	***P***[a]
	(Cases/Controls)				**(Cases/Controls)**			
	CC	**CG/GG**			**0–2**	**3–4**		
Age, month								
<60	90/120	45/54	1.12 (0.69–1.81)	0.657	80/108	55/66	1.13 (0.71–1.79)	0.612
≥60	124/155	55/51	1.35 (0.86–2.11)	0.193	116/144	63/62	1.27 (0.83–1.95)	0.273
Gender								
Female	104/117	42/47	1.01 (0.61–1.65)	0.977	94/110	52/54	1.15 (0.72–1.85)	0.559
Male	110/158	58/58	1.46 (0.94–2.26)	0.092	102/142	66/74	1.26 (0.83–1.92)	0.283
Subtypes								
Astrocytic tumors	144/275	70/105	1.31 (0.91–1.89)	0.153	137/252	77/128	1.15 (0.81–1.65)	0.431
Ependymoma	38/275	23/105	1.50 (0.85–2.67)	0.165	30/252	31/128	**1.94 (1.11–3.37)**	**0.020**
Neuronal and mixed	20/275	5/105	0.67 (0.25–1.85)	0.443	17/252	8/128	0.94 (0.40–2.25)	0.893
Embryonal tumors	10/275	2/105	0.56 (0.12–2.65)	0.465	10/252	2/128	0.44 (0.09–2.07)	0.297
Clinical stages								
I	97/275	54/105	1.47 (0.98–2.21)	0.061	91/252	60/128	1.34 (0.90–1.98)	0.148
II	52/275	21/105	1.06 (0.61–1.85)	0.840	44/252	29/128	1.30 (0.78–2.18)	0.320
III	23/275	13/105	1.37 (0.66–2.84)	0.392	19/252	17/128	1.65 (0.82–3.32)	0.157
IV	41/275	12/105	0.82 (0.41–1.65)	0.579	41/252	12/128	0.63 (0.31–1.25)	0.185
I+II	149/275	75/105	1.33 (0.93–1.90)	0.120	135/252	89/128	1.32 (0.94–1.86)	0.114
III+IV	64/275	25/105	1.05 (0.63–1.76)	0.856	60/252	29/128	0.98 (0.60–1.61)	0.938

Notes: [a]Adjusted for age and sex, omitting the corresponding stratify factor. Bold value indicates a significant relationship.
Abbreviations: CNS, central nervous system; OR, odds ratio; CI, confidence interval.

the glioma-suppressive role of FTO may through interacting with FOXO3a to promote its nuclear translocation and target gene expression.

Previous epidemiology studies have provided evidence regarding the associations of overweight/obesity related-*FTO* gene SNPs and risk of various types of cancers. For instance, SNPs rs7206790, rs9939609, rs8047395, and rs1477196, located in the intron 1 (obesity-associated region) in *FTO* gene, have been demonstrated to predispose to breast cancer. Notably, rs1477196 ranks the most significant relationship with risk of breast cancer.[26] Gaudet et al[42] genotyped 189 tagSNPs in *FTO* gene which were previously related to obesity by genome-wide association scans. However, none of the genotyped *FTO* gene SNPs could confer to risk of endometrial cancer. Sigurdson et al[25] conducted a large independent papillary thyroid cancer (PTC) case-control study in Germany. They found that *FTO* gene rs8047395 is associated with PTC risk, using samples of 422 PTC cases and 752 controls recruited from three German clinical centers. Zeng et al[43] genotyped 6 *FTO* gene SNPs (rs9939609, rs1477196, rs6499640, rs16953002, rs11075995, and rs1121980) using 537 breast cancer cases and 537 controls. Among them, *FTO* gene rs1477196 AA genotype was significantly related to decreased breast cancer risk compared to GG genotype, while rs16953002 AA genotype contributed to a higher breast cancer risk compared to GG genotype. Iles et al[27] found that variants of *FTO* gene outside of intron 1 were associated with melanoma risk. To our knowledge, no studies have assessed the association of *FTO* gene SNPs and CNS tumor risk. Considering the implications of *FTO* gene SNPs to the risk of multiple cancers, it is of significance to explore the potential value of *FTO* gene SNPs to identify populations at high risk of CNS tumor for targeted prevention. In the current study, no significant correlations were detected between *FTO* gene SNPs (rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, and rs8047395 A>G) and CNS tumor risk, either in single or combined locus analysis. In stratification analysis, carriers with 3–4 risk genotypes were more likely to develop ependymoma when compared to 0–2 risk genotypes. One possible explanation of the observation is a relatively small sample size. There may be other unknown environmental factors that also interact with the weak impact of these *FTO* SNPs and result in the observed effect.

We attempted to apply strict measurements for the investigation of a relationship between *FTO* gene SNPs and CNS tumor risk; however, the following considerations are important when interpreting the results. First, due to relatively small sample size, our study is underpowered to detect all SNPs. Second, environmental factors such as cellphone use, occupation exposures, and medical history are important to consider for CNS tumor. These variables were absent from the current study, therefore, such variables remained unaccounted. Third, though subjects from all around China, all of them were Chinese descendant. Conclusions obtained from this single population limited the generalizability to other ethnicities. Meanwhile, the underlying mechanisms of how the *FTO* gene SNPs impacts CNS tumor risk remain to be further explored in the future.

Conclusions

In all, our multi-center study identified that *FTO* gene SNPs may not have enough impact on risk of CNS tumor in a population of Chinese children. Further functional characterization is warranted to provide a more accurate picture of the biological mechanisms underlying CNS tumor susceptibility.

Acknowledgments

This work was funded by grants from the National Natural Science Foundation of China (No: 81802346, 82002636).

Disclosure

The authors have no conflicts of interest to declare.

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