ORIGINAL RESEARCH

FTO Gene Polymorphisms Contribute to the Predisposition and Radiotherapy Efficiency of Nasopharyngeal Carcinoma

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Background: Nasopharyngeal carcinoma (NPC) is mainly concentrated in East and Southeast Asia. This study aims to elucidate the potential associations of functional SNPs in the fat mass and obesity associated gene (FTO) with NPC risk and radiotherapy outcomes in a Chinese population.

Methods: Functional SNP rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, and rs8047395 A>G were genotyped and evaluated for their associations with NPC risk and radiotherapy outcomes.

Results: Both rs9939609 (allele A versus allele T: OR=1.59; 95% CI=1.17–2.17; P-value=0.003) and rs8047395 (allele G versus allele A: OR=0.76; 95% CI=0.64–0.9; P-value=0.002) were significantly associated with risk of NPC. GTEx showed risk allele A of rs9939609 and rs8047395 were significantly associated with higher FTO mRNA levels in skeletal muscle tissue, which also corroborated our findings. Meanwhile, both rs1477196 (allele A versus allele G: OR=1.64; 95% CI=1.09–2.49; P-value=0.019) and rs9939609 (allele A versus allele T: OR=0.61; 95% CI=0.43–0.87; P-value=0.006) were significantly associated with complete remission (CR) of NPC.

Conclusion: Our study identified that FTO polymorphisms contributed to the susceptibility and radiotherapy efficacy of NPC. These results shed light on the potential of establishing markers for predicting risk and personalized treatment of NPC.

Keywords: nasopharyngeal carcinoma, FTO, predisposition, radiotherapy

Introduction

Nasopharyngeal Carcinoma (NPC), a relatively rare malignant epithelial carcinoma arising from the nasopharyngeal mucosal lining, is mainly concentrated in East and Southeast Asia, the Arctic, North Africa, and the Middle East.[1–3] According to the Cancer Statistics in China, 2015, which was reported by the national office for cancer prevention and control of China, there were an estimated 60.6 thousand new NPC cases and 34.1 thousand NPC deaths annually.[4] Well established risk factors for NPC include Epstein-Barr virus (EBV) infection, consumption of salt-cured fish, family history of NPC, consumption of other cured foods, smoking, etc.[5] However, the specific mechanisms affecting the development of NPC and the effectiveness of treatment remain unclear. Thus, searching for markers of NPC predisposition and radiotherapy efficiency is of great clinical importance.

Single nucleotide polymorphisms (SNPs) have become important predictors of tumors and indicators of the effectiveness of response to radiation therapy.[6–8] SNPs

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may affect gene expression, mRNA stability, and protein function.[9] Among them, SNPs of the fat mass and obesity associated gene (FTO), the first obesity-related gene identified by genome-wide association studies (GWAS), has been linked to the occurrence, progression, and prognosis of many cancers, including breast cancer, ovarian cancer, Wilms tumor, thyroid cancer, pancreatic cancer, prostate cancer, colorectal cancer, etc.[10–19] This is because obesity plays a crucial role in the development and prognosis of cancers.[20] Further, obesity also served as an emerging driver of head and neck cancers,[21] especially central adiposity.[22] The FTO gene, which was located at 16q12.2, is a nuclear protein of the AlkB related non-haem iron and 2-oxoglutarate-dependent oxygenase superfamily.[10] It can mediate cytoplasmic m(6)Am demethy-lation in cancers.[23,24] FTO polymorphisms are significantly associated with various human diseases, especially cancers.[16,25] Among them, rs1477196, rs9939609, rs7206790, and rs8047395 are mostly explored.[16,26–30]

Whether FTO gene polymorphisms contribute to the predisposition, even radiotherapy efficiency of NPC was still unexplored. In the current study, we first performed a systematic genetic analysis to further elucidate the associations of the potential functional SNPs (rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, and rs8047395 A>G) in the FTO gene with NPC risk and radiotherapy outcomes in a Chinese population. This study will provide some novel clues to elucidate the pathogenesis of NPC and to further implement individualized radiotherapy treatment for NPC patients.

Patients and Methods
Study Subjects
In total 367 NPC cases and 380 frequency-matched healthy controls by age and gender were included in this study. All the patients underwent nasopharyngoscopy and were histologically identified as NPC, while controls with any other kind of tumors or a personal family history of NPC were excluded. The demographics and clinical characteristics of patients were collected through medical record or inquiries. Five milliliters of peripheral blood was collected. All patients received radical external irradiation with or without cisplatin-based chemotherapy or both. Efficacy was evaluated by magnetic resonance imaging (MRI) directly after the end of radiotherapy, in accordance with the efficacy evaluation criteria for solid tumors (RECIST), defining the efficacy endpoint as complete remission (CR). EBV-VCA-IgA was tested using the

ELISA kit. All procedures performed in research involving human participants were in accordance with the Declaration of Helsinki. This study was approved by the Institute committees of the School of Nursing of Chongqing medical university, and informed consent was obtained from all subjects recruited for this study.

DNA Extraction and Genotyping
Genomic DNA was extracted with the peripheral blood DNA Extraction Kit (QIAamp DNA blood Mini Kit; Qiagen, Inc., Valencia, CA). Genotyping of the four SNPs (rs1477196, rs9939609, rs7206790, and rs8047395) was conducted using the Sequenom iPLEX MassARRAY system (Sequenom, Inc., San Diego, CA, USA). For quality control, a randomly selected group of 10% of the samples was tested twice by different individuals with 100% concordance of results. All laboratory personnel were blind to the phenotype status of the samples.

Statistical Analysis
Statistical analysis was performed using SPSS 22.0 (IBM, Chicago, IL, USA), and a two-sided P-value of <0.05 was considered statistically significant. Clinical characteristics of NPC cases and healthy controls were compared by the Chi-square test or Student's t-test. The Hardy-Weinberg equilibrium (HWE) was tested by Chi-squared test to test for deviation between observed and expected frequencies among controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression model to estimate the association between the selected functional SNPs and NPC risk and radiotherapy efficiency, adjusted for the clinical characteristics.

Results
Clinical Characteristics of NPC Cases and Controls
As shown in Table 1, frequency distributions of age, gender, and drinking status were comparable in general between 367 NPC cases and 380 healthy controls (P>0.05), which indicated the adequate frequency-matching strategy. However, we found the smoking status and EBV-VCA-IgA status were significantly different between the cases and controls (P<0.001). Among the 367 NPC cases, 73% also received chemotherapy, which means 27% only received radiotherapy. For TNM stage, 34.9% were classified as I–II, while 65.1% were classified as III–IV. Of them, the radiotherapy efficacy of 254 (69.2%) patients reached CR.

Table 1 Clinical Characteristics of NPC Cases and Controls

Variables	Cases (n=367)	Controls (n=380)	*P*-value
Age	49.7±10.9	50.1±11.8	0.631
Gender			
Male	257 (70.0%)	259 (68.2%)	0.581
Female	110 (30.0%)	121 (31.8%)	
Smoking status			
Ever-smokers	154 (42.0%)	125 (32.9%)	<0.001
Non-smokers	213 (58.0%)	255 (67.1%)	
Drinking status			
Drinkers	143 (39.0%)	141 (37.1%)	0.601
Non-drinkers	224 (61.0%)	239 (62.9%)	
EBV-VCA-IgA			
Positive	241 (65.7%)	32 (8.4%)	<0.001
Negative	126 (34.3%)	348 (91.6%)	
Chemotherapy			
Yes	268 (73.0%)		
No	99 (27.0%)		
TNM stage			
I–II	128 (34.9%)		
III–IV	239 (65.1%)		
Complete remission			
Yes	254 (69.2%)		
No	113 (30.8%)		

Associations between Genetic Variations of the FTO Gene and Risk of NPC in Chinese Population

First, all four SNPs, including rs1477196, rs9939609, rs7206790, and rs8047395, were in HWE among the controls (*P*>0.05), which indicated the appropriate representativeness of the control population. As shown in Table 2, both rs9939609 (allele A versus allele T: OR=1.59; 95% CI=1.17–2.17; *P*- value=0.003) and rs8047395 (allele G versus allele A: OR=0.76; 95% CI=0.64–0.9; *P*-value=0.002) were significantly associated with risk of NPC. The results of the dominant model, recessive model, and co-additive model were all statistically significant for rs9939609 and rs8047395 (Bonferroni corrected *P*-values were still significant). Further, we summarized the risk alleles of the four SNPs together (Table 2, numbers of risk alleles ranged from 0–6). Compared with the subject with ≤3 risk alleles, those with >3 risk alleles have a non-significantly increased risk of NPC (OR=1.27; 95% CI=0.91–1.78; *P*-value=0.154).

Effect of rs9939609 and rs8047395 on FTO Gene Expression

We further analyzed the eQTL effect of rs9939609 and rs8047395 using data from GTEx to assess whether they could affect the FTO mRNA expression. As shown in Figure 1, both the risk allele A of rs9939609 and rs8047395 were significantly associated with higher FTO mRNA levels in skeletal muscle tissue (*P*-value: $4.2x10^{-6}$; $2.2x10^{-7}$, respectively).

Association between Genetic Variations of the FTO Gene and the Efficacy of Radiotherapy in NPC Patients

We also determined the associations between genetic variations of the FTO gene and the efficacy of radiotherapy in NPC patients (Table 3). Of the four SNPs, both rs1477196 (allele A versus allele G: OR=1.64; 95% CI=1.09–2.49; *P*-value=0.019) and rs9939609 (allele A versus allele T: OR=0.61; 95% CI=0.43–0.87; *P*-value=0.006) were significantly associated with CR of NPC. Results of the

Table 2 Associations between Genetic Variations of the FTO Gene and Risk of NPC

	Cases	Controls	OR (95% CI)*	*P*-value
rs1477196				
GG	215	207	1.00 (Reference)	
AG	131	140	0.94 (0.78–1.12)	0.482
AA	21	33	0.64 (0.38–1.06)	0.080
A vs G			0.86 (0.72–1.03)	0.100
Dominant			0.88 (0.71–1.09)	0.235
Recessive			0.66 (0.41–1.08)	0.101
rs9939609				
TT	256	297	1.00 (Reference)	
AG	102	80	1.54 (1.08–2.19)	0.017
AA	9	3	3.62 (1.07–12.25)	0.039
A vs T			1.59 (1.17–2.17)	0.003
Dominant			1.61 (1.15–2.27)	0.006
Recessive			3.29 (0.96–11.24)	0.058
rs7206790				
CC	249	275	1.00 (Reference)	
CG	107	98	1.25 (0.86–1.82)	0.234
GG	11	7	1.80 (0.68–4.77)	0.234
G vs C			1.28 (0.94–1.75)	0.118
Dominant			1.29 (0.91–1.84)	0.157
Recessive			1.71 (0.64–4.55)	0.280
rs8047395				
AA	163	125	1.00 (Reference)	
AG	157	194	0.65 (0.49–0.85)	0.002
GG	47	61	0.61 (0.42–0.91)	0.015
G vs A			0.76 (0.64–0.90)	0.002
Dominant			0.64 (0.49–0.83)	0.001
Recessive			0.80 (0.57–1.11)	0.186
Risk alleles				
≤3	212	238	1.00 (Reference)	
>3	155	142	1.27 (0.91–1.78)	0.154

Note: *Adjusted for age, gender, smoking status, drinking status, and EBV-VCA-IgA status.

dominant model were statistically significant for both rs9939609 and rs8047395 ($P<0.05$).

Discussion

NPC causes great pain and inconvenience to the victims. It is of great significance to explore the mechanisms related to disease prevention and carry out individualized treatment. In the current study, we explored the associations between potential functional SNPs in the FTO gene associated with NPC risk and radiotherapy outcomes in a Chinese population. We revealed that both rs9939609 and rs8047395 were significantly associated with risk of NPC. Meanwhile, rs1477196 and rs9939609 were

significantly associated with CR of NPC. To the best of our knowledge, this is the first study to reveal the essential role of FTO polymorphisms in the susceptibility and radiotherapy efficacy.

Excess body adiposity, commonly expressed as body mass index (BMI), has been identified as a risk factor for many common adult cancers.[31] FTO was both the first GWAS identified obesity-related gene and first identified N6-methyladenosine (m^6A) demethylase of eukaryotic mRNA.[10,32] In this context, a large number of studies have focused on the carcinogenic role of FTO genes and their genetic variants in the development of various malignancies.[11,33–39] A meta-analysis revealed that the
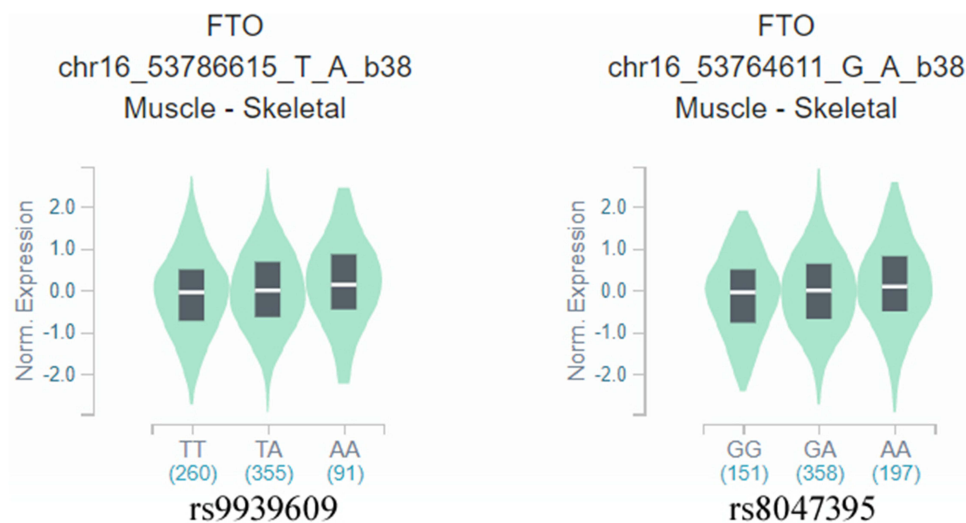
Figure 1 Genotype-based mRNA expression of the FTO gene in skeletal muscle from the GTEx portal.

significant association between FTO rs9939609 polymorphism and cancer risk was found in the homozygote model and recessive model, especially for endometrial cancer and pancreatic cancer.[25] No significant association between FTO rs8050136 polymorphism and cancer risk has also been found.[40] However, no studies have examined the role of FTO in the development of NPC to date. Only one study developed a m(6)A RNA methylation regulators-based signature (including FTO) for predicting the prognosis of head and neck squamous cell carcinoma.[41]

In the current study, we revealed that both rs9939609 and rs8047395 were significantly associated with risk of NPC. Meanwhile, GTEx showed risk allele A of rs9939609 and rs8047395 were significantly associated with higher FTO mRNA levels in skeletal muscle tissue. Considering the carcinogenic effect of FTO, the above results corroborate each other and are logical. Our result for rs8047395 was validated by a recent study about glioma, which also revealed allele A was a risk allele.[42] However, there were also two other studies about central nervous system tumors and Wilms tumors which reported null or opposite results.[13,30] We also found that rs1477196 and rs9939609 were significantly associated with CR of NPC. Previous reports showed that expression alterations of multiple m6A enzymes, including FTO, could mediate the development of resistance of cancer cells to

radiotherapy.[43] Zhou et al[44] also reported that FTO could regulate the chemo-radiotherapy resistance of cervical squamous cell carcinoma by targeting β-catenin through mRNA demethylation. Further mechanistic studies on how FTO polymorphisms influence the radiotherapy efficiency of NPC are needed.

Our study has several limitations. First, the relatively moderate sample size might preclude us from observing some weak associations, although the collection of cases has cost us a lot of effort. Second, lack of gene-environment interaction analyses due to sample size might affect the identification of clear phenotypic effects. Third, we only evaluated the radiotherapy effect of NPC and lacked long-term prognostic follow-up, which will be the focus of our next work. However, our research still reveals the important role of FTO in NPC, which will be helpful for more important research in the future.

In conclusion, our study identified that FTO polymorphisms contributed to the susceptibility and radiotherapy efficacy of NPC. These results shed light on the potential of establishing markers for predicting risk and treatment outcomes of NPC. Further functional studies of the FTO SNPs in NPC susceptibility and prognosis are warranted, which may lead to unearthing the genetic and pathophysiological mechanisms underlying this disease.

Table 3 Association between Genetic Variations of the FTO Gene and the Efficacy of Radiotherapy in NPC Patients

Variants	Complete Remission (N=254)	Non-Complete Remission (N=113)	OR (95% CI)*	P-value
rs1477196				
GG	145	78	1.00 (Reference)	
AG	95	32	1.66 (1.01–2.74)	0.047
AA	14	3	2.61 (0.76–8.94)	0.127
A vs G			1.64 (1.09–2.49)	0.019
Dominant			1.74 (1.08–2.82)	0.023
Recessive			2.22 (0.64–7.71)	0.207
rs9939609				
TT	187	70	1.00 (Reference)	
AG	63	36	0.62 (0.4–0.95)	0.028
AA	4	7	0.31 (0.09–0.99)	0.049
A vs T			0.61 (0.43–0.87)	0.006
Dominant			0.58 (0.39–0.89)	0.011
Recessive			0.36 (0.11–1.16)	0.087
rs7206790				
CC	167	82	1.00 (Reference)	
CG	78	29	1.37 (0.8–2.37)	0.254
GG	9	2	2.30 (0.5–10.49)	0.283
G vs C			1.42 (0.89–2.25)	0.139
Dominant			1.43 (0.85–2.41)	0.176
Recessive			2.12 (0.46–9.76)	0.335
rs8047395				
AA	111	52	1.00 (Reference)	
AG	113	44	1.25 (0.72–2.18)	0.428
GG	30	17	0.86 (0.51–1.44)	0.565
G vs A			1.02 (0.76–1.36)	0.899
Dominant			1.14 (0.63–2.09)	0.665
Recessive			0.79 (0.47–1.33)	0.369

Note: *Adjusted for age, gender, smoking status, drinking status, EBV-VCA-IgA status, TNM stage, and Chemotherapy.

Disclosure

The authors declare that they have no conflicts of interest.

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