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ORIGINAL RESEARCH

Associations Between *FTO* Polymorphisms and Neuroblastoma Risk in Chinese Children

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Background: Neuroblastoma (NB) is a malignancy of neural crest cells that primarily affects children. Single nucleotide polymorphisms (SNPs) in the fat mass and obesity-associated (*FTO*) gene, a well-conserved gene, have been implicated in tumorigenesis. However, there is currently insufficient evidence to establish the relationship between *FTO* gene SNPs and susceptibility to NB.

Methods: A TaqMan assay was conducted to examine the potential associations between *FTO* gene SNPs and the risk of NB in a cohort of 898 patients and 1734 controls from eight medical centers in China. Additionally, stratification analysis was performed to evaluate the relationship between the selected *FTO* SNPs and the susceptibility to NB among various subgroups.

Results: No significant association was found between the selected *FTO* polymorphisms and the risk of NB in either the single locus analysis or the combined analysis.

Conclusion: However, our study reveals that individuals with retroperitoneal NB and those with stage III+IV NB are more prone to exhibit *FTO* SNPs compared to other patients. Moreover, participants with the *FTO* rs8047395 GG genotype displayed a higher likelihood of developing stage III+IV NB in comparison to other participants.

Keywords: *FTO*, single nucleotide polymorphisms, neuroblastoma, susceptibility

Introduction

Neuroblastoma (NB) is the most common pediatric extracranial solid tumor that develops from the sympathetic nervous system.[1,2] NB accounts for approximately 8% of all pediatric cancers.[3] Furthermore, the prognosis of NB varies depending on the heterogeneity in age, clinical stage, genetic features, and biological characteristics.[1,4,5] Additionally, patients diagnosed with neonatal NB and low-risk NB generally exhibit a more favorable prognosis,[3,6] whereas those with high-risk NB commonly develop metastases and experience a rapid deterioration of their condition. The 5-year survival rate for patients with high-risk NB is less than 50%.[7–9] Consequently, there is an urgent need to identify novel therapies for patients with NB.

With the progress of high-throughput "omics" techniques, several genes and molecules have undergone evaluation as potential targets for the treatment of NB. Additionally, certain genetic SNPs, such as the *YTHDC1* gene polymorphism (rs3813832 T>C)[10] and the *hOGG1* gene polymorphism (rs1052133 G>C),[11] have been linked to NB susceptibility.

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Nevertheless, our current understanding of the correlation between *FTO* SNPs and NB susceptibility remains limited. Notably, certain *FTO* SNPs situated within intron 1 of the *FTO* gene have demonstrated a significant influence on body mass and obesity in humans.[12–14]

In a recent study, the overexpression of *FTO* was discovered to play a critical role in acute myeloid leukemia as an N6-methyladenosine (m^6A) demethylase. It was observed to promote cell proliferation and transformation while suppressing apoptosis.[15] Furthermore, aberrant *FTO* overexpression was associated with the promotion of breast tumor progression,[16] regulation melanoma tumorigenesis as a pro-tumorigenic factor,[17] and the proliferation and invasion of colorectal cancer cells, while also suppressing their apoptosis.[18] Additionally, *FTO* knockdown led to a decrease in proliferation of N2a NB cells.[19] Lin et al also reported that *FTO* overexpression could modulate energy homeostasis through the cAMP-response element binding protein signaling pathway in human NB cells.[20]

Considering the significance of *FTO*, we performed a case-control study to investigate the association between *FTO* polymorphisms and the risk of NB.

Materials and Methods

Study Population

This retrospective case-control study enrolled all unrelated patients of Chinese Han ethnicity with NB from eight medical centers in Guangzhou, Zhengzhou, Wenzhou, Xi'an, Taiyuan, Kunming, Changsha, and Shenyang (Table S1), following the same inclusion criteria. In addition, 1734 NB-free controls matched for age, sex, and ethnicity were recruited from the same geographical locations during the same period. The case group consisted of 898 patients who were diagnosed with NB based on precise diagnostic criteria using clinical and histopathological evidence and received treatment at these eight medical centers. The detailed inclusion criteria have been previously reported in our studies.[21,22]

Polymorphism Selection and Genotyping

Four potential *FTO* SNPs (rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, rs8047395 A>G) were retrieved from the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP) and the SNPinfo Web Server (https://snpinfo.niehs.nih.gov) based on our previous studies.[22–24] The selection criteria were as follows: Firstly, SNPs are located in the 5'-flanking regions, 3'- and 5'- untranslated regions, and exons of the *FTO* gene. Moreover, the minor allele frequencies should be >5% in Chinese Han population; Furthermore, LDmatrix Tool (https://ldlink.nih.gov) result indicated that there was no significant linkage disequilibrium (LD) among each other ($R^2 < 0.8$). As shown in the Figure S1, there was no significant LD among these four SNPs of FTO ($R^2 = 0.064$ between rs7206790 and rs8047395, $R^2 = 0.034$ between rs7206790 and rs1477196, $R^2 = 0.536$ between rs7206790 and rs9939609, $R^2 = 0.598$ between rs8047395 and rs1477196, $R^2 = 0.089$ between rs8047395 and rs9939609, and $R^2 = 0.06$ between rs1477196 and rs9939609). Genomic DNA was then extracted from the patients' peripheral blood using standard procedures, and the SNP types were determined using a commercial TaqMan real-time polymerase chain reaction kit.[25,26] Additionally, approximately 10% of the DNA samples were randomly selected for re-genotyping using sequencing to ensure quality control and verify the accuracy of the results. The concordance between the two sets of results was 100%, demonstrating high reproducibility.

Statistical Analysis

The goodness-of-fit chi-square (χ^2) test was conducted to assess whether the frequency distributions of the selected SNP genotypes adhered to the Hardy-Weinberg equilibrium (HWE) in the control group. Two-sided χ^2-tests were used to compare demographic variables and allele frequency distributions between NB patients and controls. The odds ratio (OR), 95% confidence interval (CIs), and adjusted *P* values for age and sex were calculated for each *FTO* SNP. Unconditional univariate and multivariate logistic regression analyses were performed to evaluate the strength of the association between the selected SNPs and NB susceptibility, providing ORs and 95% CIs. Furthermore, stratification analyses were conducted based on age, sex, original tumor location, and International Neuroblastoma Staging System (INSS) stages. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC). The detailed SAS running codes are provided in the supplementary materials (SAS Code 1 and SAS Code 2). Statistical significance was set at $P<0.05$.

Results

Correlations Between FTO SNPs and NB Susceptibility

A total of 888 patients with NB and 1733 controls were successfully genotyped. The genotype frequency distributions of the four *FTO* SNPs (rs1477196 G>A, rs9939609 T>A, rs7206790 C>G, rs8047395 A>G) in patients with NB and controls, along with their relevance to NB susceptibility are presented in Table 1. Additionally, the genotype frequencies of the four selected SNPs accorded with the Hardy-Weinberg equilibrium (HWE) in controls (HWE=0.466 for rs1477196 G>A, HWE=0.046 for rs9939609 T>A, HWE=0.022 for rs7206790 C>G, and HWE=0.657 for rs8047395 A>G). Consequently, no significant associations were observed between the selected *FTO* polymorphisms and the risk of NB in the single locus analysis (*P* adjusted for age and sex >0.05).

Table 1 Association Between FTO Gene Polymorphisms and Neuroblastoma Risk

Genotype	Cases (N=888)	Controls (N=1733)	*P* [a]	Crude OR (95% CI)	*P*	Adjusted OR (95% CI) [b]	*P* [b]
rs1477196 G>A (HWE=0.466)							
GG	485 (54.62)	952 (54.93)		1.00		1.00	
GA	327 (36.82)	657 (37.91)		0.98 (0.82–1.16)	0.790	0.97 (0.82–1.16)	0.763
AA	76 (8.56)	124 (7.16)		1.20 (0.89–1.63)	0.236	1.18 (0.87–1.60)	0.290
Additive			0.511	1.04 (0.92–1.19)	0.510	1.04 (0.91–1.18)	0.582
Dominant	403 (45.38)	781 (45.07)	0.878	1.01 (0.86–1.19)	0.878	1.01 (0.86–1.19)	0.935
Recessive	812 (91.44)	1609 (92.84)	0.200	1.21 (0.90–1.64)	0.201	1.19 (0.89–1.61)	0.247
rs9939609 T>A (HWE=0.046)							
TT	648 (72.97)	1297 (74.84)		1.00		1.00	
TA	220 (24.77)	393 (22.68)		1.12 (0.93–1.36)	0.241	1.13 (0.93–1.36)	0.218
AA	20 (2.25)	43 (2.48)		0.93 (0.54–1.60)	0.795	0.94 (0.55–1.61)	0.814
Additive			0.428	1.07 (0.91–1.25)	0.428	1.07 (0.91–1.26)	0.393
Dominant	240 (27.03)	436 (25.16)	0.301	1.10 (0.92–1.32)	0.301	1.11 (0.92–1.33)	0.273
Recessive	868 (97.75)	1690 (97.52)	0.717	0.91 (0.53–1.55)	0.717	0.91 (0.53–1.56)	0.732
rs7206790 C>G (HWE=0.022)							
CC	654 (73.65)	1255 (72.42)		1.00		1.00	
CG	217 (24.44)	425 (24.52)		0.98 (0.81–1.18)	0.832	0.99 (0.82–1.19)	0.893
GG	17 (1.91)	53 (3.06)		0.62 (0.35–1.07)	0.067	0.61 (0.35–1.07)	0.084
Additive			0.262	0.91 (0.78–1.07)	0.262	0.92 (0.78–1.08)	0.285
Dominant	234 (26.35)	478 (27.58)	0.503	0.94 (0.78–1.13)	0.503	0.95 (0.79–1.14)	0.547
Recessive	871 (98.09)	1680 (96.94)	0.086	0.62 (0.36–1.08)	0.089	0.62 (0.35–1.07)	0.085
rs8047395 A>G (HWE=0.657)							
AA	348 (39.19)	683 (39.41)		1.00		1.00	
AG	393 (44.26)	803 (46.34)		0.96 (0.81–1.15)	0.655	0.96 (0.80–1.14)	0.619
GG	147 (16.55)	247 (14.25)		1.17 (0.92–1.49)	0.208	1.15 (0.90–1.47)	0.257
Additive			0.380	1.05 (0.94–1.18)	0.380	1.05 (0.93–1.18)	0.448
Dominant	540 (60.81)	1050 (60.59)	0.912	1.01 (0.86–1.19)	0.912	1.00 (0.85–1.18)	0.982
Recessive	741 (83.45)	1486 (85.75)	0.119	1.19 (0.96–1.49)	0.119	1.18 (0.94–1.47)	0.149
Combine risk genotypes[c]							
0	8 (0.90)	24 (1.38)	0.055	1.00		1.00	
1	20 (2.25)	46 (2.65)		1.30 (0.50–3.40)	0.587	1.34 (0.51–3.49)	0.550
2	706 (79.50)	1414 (81.59)		1.50 (0.67–3.35)	0.326	1.52 (0.68–3.40)	0.309
3	86 (9.68)	129 (7.44)		2.00 (0.86–4.66)	0.108	2.02 (0.87–4.70)	0.104
4	68 (7.66)	120 (6.92)		1.70 (0.72–3.99)	0.223	1.69 (0.72–3.98)	0.227
0–2	734 (82.66)	1484 (85.63)		1.00		1.00	
3–4	154 (17.34)	249 (14.37)	0.046	1.25 (1.004–1.56)	0.046	1.24 (0.99–1.54)	0.060

Notes: [a]χ^2 test for genotype distributions between neuroblastoma patients and cancer-free controls. [b]Adjusted for age and sex. [c]Risk genotypes were rs1477196 AA, rs9939609 TT/TA, rs7206790 CC/CG, and rs8047395 GG.

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To delve deeper into the relationship between *FTO* SNPs and NB susceptibility, the combined effect of risk genotypes was examined (Table 1). However, the findings from the combined analysis (*P* adjusted for age and sex >0.05) were identical to those of the single locus analysis.

Stratification Analysis

To further evaluate the association between the selected *FTO* polymorphisms and NB susceptibility among different subgroups, stratification analysis was conducted based on age, sex, site of origin, and INSS stage (Table 2). Single locus stratification analysis revealed no correlation between the rs7206790 C>G polymorphism and the risk of NB in any of the subgroups. However, among participants in the INSS stage III+IV subgroup, those with the GG genotype of rs8047395 A>G had a significantly higher susceptibility to NB compared to those with the AA/AG genotype (Adjusted OR=1.36, 95% CI=1.01–1.81, *P*=0.040). Furthermore, combined analysis indicated that the presence of 3–4 risk genotypes had a significantly correlation with NB originating in retroperitoneal (AOR=1.47, 95% CI=1.08–2.00, *P*=0.015) and NB in III +IV INSS stages (AOR=1.37, 95% CI=1.03–1.83, *P*=0.033) compared with the reference group.

Discussion

The *FTO* gene is situated on 16q12.2 and is responsible for producing the FTO protein, It has been reported *FTO* knockdown led to increased amounts of N^6-methyladenosine (m^6A) in mRNA, whereas overexpression of FTO resulted in decreased amounts of m^6A in vitro, which strongly suggested FTO plays a crucial role in the demethylation process of N6-methyladenosine (m^6A) residues in nuclear RNA within human cells.[27,28] Several studies have shown that m^6A modification is associated with various aspects of tumor biology, including growth,[29] proliferation,[30] differentiation,[31] invasion,[32] and metastasis.[33] Additionally, it has been observed that m^6A can function both as a tumor stimulator and a tumor repressor.[34,35] Owing to its oxidative demethylation function, the biological regulatory mechanism of *FTO* expression has been recently explored in various human malignancies, such as breast tumors,[36] bladder tumors,[37] prostate cancer,[38] hepatocellular carcinoma,[39] and non-small cell lung carcinoma.[40] Furthermore, the impact of *FTO* SNPs on tumorigenesis, tumor progression, and cancer susceptibility has also been revealed.[41] Gaudet et al concluded that the rs8050136 C>A *FTO* polymorphism did not have a significant impact on the risk of endometrial cancer in the Polish Endometrial Case-Control Study,[42] and this finding was consistent with three replication studies conducted by the same authors.[42] In a hospital-based case-control study by Tang et al,[43] it was reported that the *FTO* SNPs rs8050136 C>A and rs9939609 T>A polymorphisms were significantly associated with the risk of pancreatic cancer. This study included 1070 patients with pancreatic cancer and 1175 cancer-free controls.

There are many studies on the relationship between m^6A modification and nervous system tumors, however, studies on FTO and nervous system tumors are limited. Cui et al confirmed that overexpression of FTO promoted glioblastoma stem cell-induced tumorigenesis as well as shortened the life-span of GSC-engrafted mice.[44] This finding established a causative link between m^6A modifications and glioblastoma, a highly aggressive form of brain cancer. NB, as an embryonal tumor originating from the nervous system,[45,46] has a high incidence rate among infants.[47,48] Recently, the involvement of m^6A modification in NB has been elucidated. Cheng et al proposed that miR-98 binds to the 3'-UTR of *MYCN* RNA and down-regulates its expression through m^6A modification, thereby inhibiting NB progression.[49] Wang et al reported that five m^6A modification-related genes, namely *METT14, WTAP, HNRNPC, YTHDF1* and *IGF2BP2*, could impact the clinical prognosis of NB.[50] Zeng et al have confirmed the relationship between an SNP (rs3738067 A>G) of the m^6A modification-related gene *YTHDF2* and NB susceptibility.[51] Several studies have reported the results of the correlation between FTO and NB, most of which revealed the role of FTO in human neuroblastoma cells, such as SH-SY5Y cells and SK-N-SH cells. Hu et al reported that Early B Cell Factor 3 (EBF3), a member of the highly evolutionarily conserved EBF-transcription factor family, whose m^6A methylation modification level and mRNA half-life were upregulated by FTO siRNA, and EBF3 overexpression suppressed apoptosis of SH-SY5Y cells.[52] In N-methyl-4-phenylpyridinium treated SH-SY5Y cells, FTO impaired the NRF2 mRNA stability via m6 A-dependent pathway to led to the ferroptosis significantly upregulated.[53] And FTO increased NRF2 expression by mediating m^6A demethylation of NRF2 mRNA, thereby inhibiting oxidative stress response in glucose deprivation/re-oxygenation (OGD/R)-induced SH-SY5Y cells.[54] Lin et al have confirmed FTO interacted with CaMKII and modulated the activity of CREB signaling pathway in SK-N-SH cells, and the CREB signaling pathway could regulate food intake and energy homeostasis.[20] Moreover, Lin et al have

Table 2 Stratification Analysis for the Association Between Risk Genotypes and Neuroblastoma Risk

Variables	rs7206790 (cases/controls)		AOR (95% CI)[a]	*P*[a]	rs8047395 (cases/controls)		AOR (95% CI)[a]	*P*[a]	Risk genotypes (cases/controls)		AOR (95% CI)[a]	*P*[a]
	CC/CG	GG			AA/AG	GG			0–2	3–4		
Age, month												
≤18	334/692	7/21	0.71 (0.30–1.68)	0.432	291/631	50/82	1.32 (0.90–1.92)	0.155	290/629	51/84	1.31 (0.90–1.91)	0.155
>18	537/988	10/32	0.58 (0.28–1.19)	0.137	450/855	97/165	1.11 (0.84–1.47)	0.448	444/855	103/165	1.20 (0.91–1.58)	0.188
Sex												
Females	398/716	7/28	0.46 (0.20–1.06)	0.067	340/640	65/104	1.15 (0.82–1.61)	0.420	337/639	68/105	1.20 (0.86–1.68)	0.280
Males	473/964	10/25	0.81 (0.39–1.70)	0.579	401/846	82/143	1.20 (0.89–1.62)	0.226	397/845	86/144	1.26 (0.94–1.69)	0.120
Sites of origin												
Adrenal gland	242/1680	5/53	0.66 (0.26–1.66)	0.373	209/1486	38/247	1.06 (0.73–1.54)	0.750	209/1484	38/249	1.05 (0.73–1.53)	0.781
Retroperitoneal	310/1680	4/53	0.40 (0.15–1.13)	0.083	255/1486	59/247	1.37 (1.00–1.87)	0.053	251/1484	63/249	**1.47 (1.08–2.00)**	**0.015**
Mediastinum	203/1680	7/53	1.05 (0.47–2.34)	0.907	184/1486	26/247	0.85 (0.55–1.32)	0.473	184/1484	26/249	0.85 (0.55–1.30)	0.446
Others	104/1680	1/53	0.30 (0.04–2.18)	0.232	86/1486	19/247	1.37 (0.81–2.29)	0.238	83/1484	22/249	1.62 (0.99–2.65)	0.054
INSS stages												
I+II+4s	458/1680	9/68	0.61 (0.30–1.25)	0.178	400/1486	67/247	1.02 (0.76–1.36)	0.902	394/1484	73/249	1.12 (0.84–1.48)	0.449
III+IV	380/1680	8/68	0.65 (0.30–1.38)	0.261	314/1486	74/247	**1.36 (1.01–1.81)**	**0.040**	313/1484	75/249	**1.37 (1.03–1.83)**	**0.033**

Notes: [a]Adjusted for age and sex, omitting the corresponding stratification factor. Bold values indicate statistically significant associations (AOR > 1 with 95% CI excluding 1; $P < 0.05$).
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

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demonstrated FTO overexpression inhibited cell proliferation, whereas FTO knockdown promoted cell proliferation in NB cells, and the sensitivity of NB cells to chemotherapeutic drugs (etoposide and paclitaxel) is contributed to FTO expression level.[55] Those study mentioned above showed that FTO expression was correlated with survival probability and prognostic factors in patients with NB. Consequently, it is reasonable to hypothesize that *FTO* SNPs may influence one or more pathological processes involved in the occurrence, progression, deterioration, or metastasis of NB. Limited studies have demonstrated the association between *FTO* SNPs and the susceptibility, tumorigenesis, and progression of pediatric NB. Nevertheless, this hospital-based case-control study represents the first attempt, to our knowledge, to assess the impact of *FTO* SNPs on NB susceptibility in the Chinese Han population. Our findings indicate that the selected *FTO* polymorphisms did not show a significant correlation with NB susceptibility overall. However, in the stratification analysis of *FTO* rs8047395 A>G, we observed that patients with a GG genotype in the stage III+IV subgroup were considered to have a higher risk of NB, therefore the results of our study may contribute to the effective health risk assessment of possible NB patients.

Our study has several limitations that should be acknowledged. Firstly, the study population may not be entirely representative of the entire Chinese population, despite being the largest case-control study conducted to evaluate the association between *FTO* SNPs and NB susceptibility specifically in the Chinese Han population. Therefore, further studies with larger sample sizes are needed to confirm and validate our findings. Additionally, the low incidence rate of NB poses challenges in conducting studies with small sample sizes, which may introduce some degree of bias. Furthermore, it is crucial to recognize that tumor susceptibility is influenced by a complex interplay between genetic risk factors and environmental factors.[56] Furthermore, we did not evaluate important environmental factors, such as dietary habits, physical fitness, and childhood exposures, which could have a profound effect on the statistical analysis outcomes. Additionally, our study only focused on four specific *FTO* SNPs, limiting our ability to elucidate the role of all *FTO* polymorphisms in NB. Therefore, it is essential to identify potentially functional *FTO* polymorphisms to establish comprehensive associations between other *FTO* SNPs and NB susceptibility. Ultimately, mechanistic research and functional analysis will be fundamental approaches to confirm and clarify the underlying mechanisms linking *FTO* polymorphisms to NB susceptibility.

In summary, our study did not identify any remarkable associations between the selected *FTO* polymorphisms and NB susceptibility. However, our findings lay the groundwork for future research exploring the role of *FTO* SNPs in NB. Given the clinical significance of the relationship between *FTO* SNPs and NB susceptibility, larger-scale mechanistic studies are warranted to deepen our understanding and improve the treatment of NB.

Abbreviation

NB, Neuroblastoma; SNPs, Single nucleotide polymorphisms; m^6A, N6-methyladenosine; HWE, Hardy–Weinberg equilibrium; CIs, confidence interval; INSS, International Neuroblastoma Staging System.

Data Sharing Statement

All data generated or analyzed during this study are included in this manuscript.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the parents or guardians of all participants included in the study. The experimental protocol adhered to the ethical guidelines outlined in the Helsinki Declaration. Approval for this study was granted by the ethics committees of each clinic medical center, namely Shengjing Hospital of China Medical University, Hunan Children's Hospital, Kunming Children's Hospital, the Second Affiliated Hospital of Xi'an Jiaotong University, Children Hospital and Women Health Center of Shanxi, the First Affiliated Hospital of Zhengzhou University, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Guangzhou Women and Children's Medical Center.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

This paper is also available on Authorea (www.authorea.com) as a preprint Hyperlink with DOI: 10.22541/au.168127385.58258722/v1. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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