



Gene Polymorphisms of m6A Erasers FTO and ALKBH1 Associated with Susceptibility to Gastric Cancer

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Purpose: Fat mass and obesity-associated protein (FTO) and AlkB homolog 1 (ALKBH1) are m6A demethylases that have been demonstrated to be associated with the overall survival of patients with gastric cancer (GC). This study investigates the influence of genetic variants of *FTO* and *ALKBH1* on susceptibility to GC.

Patients and Methods: Potentially functional single nucleotide polymorphisms (SNPs) of *FTO* and *ALKBH1* were genotyped in 419 patients with GC and 569 healthy controls by Kompetitive allele-specific PCR.

Results: The AG and AG/AA variants of *FTO* rs2287142 were significantly associated with a decreased GC risk (for AG/AA vs GG: adjusted OR = 0.73, $p = 0.020$). The GA and GA/GG variants of *ALKBH1* rs1076496 were closely correlated with an increased risk of GC in people aged ≥ 55 years (for GA/GG vs AA: adjusted OR = 1.51, $p = 0.041$) but showed a decreasing tendency of risk of GC in people aged < 55 years (adjusted OR = 0.85, $p = 0.444$). *FTO* rs2287142 and *ALKBH1* rs1076496 conformed to the principle of a dominant model. *FTO* haplotype rs1421091-rs1421092-rs2287142-rs9939609 CTAT was closely associated with a lower risk of total GC (adjusted OR = 0.62, $p = 0.023$), while CTGA was linked with an increased risk of intestinal GC (adjusted OR = 2.51, $p = 0.005$). *ALKBH1* rs1048147-rs1076496-rs11159286 CAC haplotype was significantly associated with a decreased risk of GC in people aged ≥ 55 years (adjusted OR = 0.41, $p = 0.008$). The *FTO* rs2287142-rs9939609 AG/AA-TT combination was associated with a decreased risk of GC only in the presence of rs1421091 TC/TT (adjusted OR = 0.70, $p = 0.047$), demonstrating that these *FTO* SNPs might have a cooperative effect on susceptibility to GC.

Conclusion: *FTO* and *ALKBH1* SNPs may have predictive value in evaluating susceptibility to GC with differing age or Lauren classification.

Keywords: *FTO*, *ALKBH1*, gastric cancer, susceptibility, Lauren classification

Introduction

Gastric cancer (GC) is one of the most common digestive malignancies worldwide.^{1,2} The carcinogenesis process of GC involves an evolution from an inflammatory to a precancerous stage, and finally to the carcinoma.^{3,4} Marked genetic heterogeneity may play a crucial role in this process, along with *Helicobacter pylori* infection, lifestyle, and other risk factors.^{5,6}

N6-methyladenosine (m6A) is one of the most deeply studied RNA modifications in eukaryotic cells and is involved in multiple aspects of RNA metabolism, such as RNA decay, RNA nuclear export, mRNA translation, and mRNA stability.⁷ With increasing evidence demonstrating that m6A plays a key role in cancers, the “writers”, “erasers”, and “readers” that add, remove, or bind to m6A sites, respectively, have also garnered interest of the research community.⁸ In our previous study, we explored the associations of a series of proteins expressed by m6A-related genes with GC and

found that a decreased level of fat mass and obesity-associated protein (FTO) was markedly associated with a shorter overall survival of patients with GC, and a lower expression of AlkB homolog 1 (ALKBH1) was correlated with larger tumor size (≥ 5 cm) and more advanced TNM stages of GC.⁹

FTO and ALKBH1 are primary m6A demethylases that are capable of reversing the methylation of RNA by oxidizing the *N*-methyl group of m6A sites to a hydroxymethyl group.^{10,11} As implied by the name, the *FTO* gene is located in the obesity susceptibility loci determined by a 2007 genome-wide association study.^{12,13} The most typical single nucleotide polymorphism (SNP) rs9939609, along with many other SNPs, such as rs8050136, rs1121980, and rs17817449, in the intron 1 region of *FTO* have been reported to affect the risk of obesity.^{14–16} The risk allele A of *FTO* rs9939609 was closely related to obesity and BMI across different populations such as Chinese, Brazilians, and Iranians.^{17–19} Moreover, several SNPs of *FTO*^{20,21} and one SNP located downstream of *ALKBH1*²² have been demonstrated to be strongly related with the occurrence and development of cancers.

To our knowledge, the influence of genetic polymorphisms of *FTO* and *ALKBH1* on the risk of GC has not been previously investigated. In the present study, we selected and genotyped potentially functional SNPs of *FTO* and *ALKBH1* in 419 Chinese patients with GC and 569 healthy controls, and the individual and interactive genetic effects of genetic polymorphisms of *FTO* and *ALKBH1* on susceptibility to GC were comprehensively explored.

Materials and Methods

Participants

This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (Guangzhou, China) (approval NO. G2022-002-01). Written informed consent was provided by all participants at their first visit. All experiments were performed in accordance with the guidelines stated in the Declaration of Helsinki. In total, 988 subjects, which included 419 patients with GC and 569 healthy individuals, had been retrospectively recruited from the Sun Yat-sen University Cancer Center between July 2011 and June 2016. The diagnosis and Lauren classification of GC was confirmed by surgery, followed by pathological examination. The medical records were carefully reviewed to obtain demographic parameters. Healthy participants visiting for a physical check would be included if they had no history of precancerous lesions or other malignant or serous systemic diseases.

SNP Selection

Candidate SNPs were selected using tools from the SNPinfo Web Server (<http://snpinfo.niehs.nih.gov/>). Flanking sequences 5000 bp upstream and 1000 bp downstream of *FTO* and *ALKBH1* genes were separately searched among the Han Chinese in Beijing, China and the SNPs annotated with functions such as nonsynonymous SNP, splicing regulation, stop codon, PolyPhen prediction, transcriptional factor binding site (TFBS), and microRNA binding site, and the nearby genes were screened. The SNPs with minor allele frequency < 0.05 were excluded. In addition, *FTO* rs9939609 was added to the candidate list because it has been reported to be linked with risk of cancer in a series of studies.²¹

Genotyping Assay

Genomic DNA was isolated from peripheral blood lymphocytes using the phenol-chloroform method and diluted to a working concentration of 50 ng/ μ L before genotyping. All sample DNAs were randomized on 384-well plates and blinded for the disease status. Genotyping was conducted using Kompetitive allele-specific PCR (KASP) by Gene Company (Shanghai, China) as described in previous publications.^{23,24} In brief, this procedure involved adding the SNP-specific KASP Assay mix and the universal KASP Master mix to DNA samples that were then subjected to a thermal cycling reaction (Table S1) followed by an end-point fluorescent read using a PHERAstar FSX Microplate Reader (BMG Labtech, Ortenberg, Germany). The KASP Assay mix contained three assay-specific non-labelled oligos, two allele specific forward primers, and one common reverse primer designed specific to each allele of the SNP (Table S2). For quality control, 10% of the total samples were repeatedly genotyped and the concordance rate reached 100%.

Determining the Optimal Genetic Models

With A defined as the variant allele and B as the common allele, odds ratio 1 (OR1) was determined for AA versus BB, OR2 for AB versus BB, and OR3 for AA versus AB. These three pairwise comparisons were evaluated to determine the best genetic models for candidate SNPs, as reported in a previous publication:²⁵ (1) If $OR1 = OR3 \neq 1$ and $OR2 = 1$, then a recessive model was considered and AA was compared with AB plus BB; (2) if $OR1 = OR2 \neq 1$ and $OR3 = 1$, then a dominance model was used and AA plus AB was compared with BB; (3) if $OR2 = 1/OR3 \neq 1$ and $OR1 = 1$, then a complete overdominance model was considered and AB was compared with AA plus BB; and (4) if $OR1 > OR2 > 1$ and $OR1 > OR3 > 1$ (or $OR1 < OR2 < 1$ and $OR1 < OR3 < 1$), then a codominance model was considered and AA was compared with AB and with BB.

Statistical Analysis

The association of each SNP with the risk of GC was explored by multivariate logistic regression, with or without adjusting for sex and age, and was recorded as OR with 95% confidence interval (CI). To explore the modifying effects of sex and age on the influence of candidate SNPs on the risk of GC, we used the Breslow–Day test, which is commonly used to test for homogeneity by comparing the differences between the ORs from each stratum. The cooperative effect of SNP-A on SNP-B was explored by comparing the associations between SNP-B and GC by a multivariate logistic regression analysis adjusted for sex and age when all data was grouped according to the two different genotypes of SNP-A. All statistical analyses were performed using the SPSS 17.0 software (SPSS, Chicago, IL, USA), excluding the calculations of D' and r^2 values for linkage disequilibrium (LD) and the haplotype analysis, which were performed using an online tool (<https://www.snpstats.net/start.htm>). Each haplotype with a minimum frequency of 0.03 in the control group was explored using the common haplotype as the reference. All p values were two-sided and statistical significance was set at $p < 0.05$.

Results

Individual Genetic Effects of Candidate SNPs on the Risk of GC

Four SNPs of *FTO* and three SNPs of *ALKBH1* predicted to have potential function were chosen and genotyped (Table 1). The clinicopathological features of the studied population are presented in Table 2. We investigated the existence of individual associations between the seven SNPs and the total risk of GC, which were evaluated by crude ORs and adjusted ORs while controlling by sex and age. We then explored the potential influence of modification factors on the candidate SNPs. Regardless of performing a crude analysis or adjusted analysis, *FTO* rs2287142 AG (adjusted OR = 0.73, 95% CI: 0.55–0.96, $p = 0.025$) and AG/AA (adjusted OR = 0.73, 95% CI: 0.56–0.95, $p = 0.020$) genotypes were both significantly associated with a lower risk of GC compared with that of the GG genotype, while the other SNPs did not show any individual effects on susceptibility to GC (Table 3).

Considering the discrepant genetic background for GC with differing Lauren classification, we further grouped patients with GC into intestinal, diffuse, and mixed-type subgroups. Due to a very limited sample size in each subgroup (intestinal type, 128; diffuse type, 151; and mixed type, 116), this part of the analysis was regarded as a preliminary

Table 1 Basic Information of SNPs Explored in the Present Study

Gene/Locus	SNP	Chromosome	Location	Reference Allele	Alternative Allele	Function Annotation
<i>FTO</i>	rs1421091	16	53739773	C	A	TFBS
<i>FTO/RPGRIP1L</i>	rs1421092	16	53734221	C	T	TFBS
<i>FTO</i>	rs2287142	16	53945351	G	A	Splicing (ESE or ESS)
<i>FTO</i>	rs9939609	16	53820527	T	A	None
<i>ALKBH1</i>	rs1048147	14	78139988	C	A	miRNA binding site
<i>ALKBH1/SLIRP</i>	rs1076496	14	78176851	A	G	TFBS
<i>ALKBH1/SLIRP</i>	rs11159286	14	78174473	C	A	Splicing

Abbreviations: ESE or ESS, exonic splicing enhancer or silencer; SNP, single nucleotide polymorphism; TFBS, transcription factor binding site.

Table 2 The Clinicopathological Characteristics of Studied Population

Variable		Healthy Control	Gastric Cancer	p value
N		569	419	
Sex	Male	439 (77.2%)	322 (76.8%)	0.911
	Female	130 (22.8%)	97 (23.2%)	
Age (Mean \pm SD, years)		52.8 \pm 15.3	56.8 \pm 11.0	< 0.001
	≥ 55	263 (46.2%)	260 (62.1%)	
	< 55	306 (53.8%)	159 (37.9%)	
Lauren's classification	Intestinal type		128 (30.6%)	
	Diffuse type		151 (36.0%)	
	Mixed type		116 (27.7%)	
	Unclear		24 (5.7%)	

Abbreviations: N, number; SD, standard deviation.

exploration. After gender- and age-adjusted analysis, we observed borderline associations between *ALKBH1* rs1048147 and the risk of mixed-type GC (AC/AA vs CC: OR = 1.54, 95% CI: 1.02–2.33, $p = 0.042$), and between *FTO* rs1421092 and the risk of intestinal type GC (TT vs TC/CC: OR = 1.59, 95% CI: 1.02–2.48, $p = 0.042$). No statistical association was found between these variants and diffuse type GC.

Influence of Candidate SNPs Modified by Sex and Age on the Risk of GC

There were no differences between ORs in males and females for all the investigated SNPs (all Breslow–Day test p values > 0.05, Table 4), which indicated no modifying effect of sex on these SNPs. The *FTO* rs2287142 AG and AG/AA genotypes were still statistically related to a low risk of GC under the modifying effects of sex and age (Tables 4 and 5).

Interestingly, the associations of the *ALKBH1* rs1076496 GA genotype with risk of GC were significantly different between young (< 55 years) and elderly people (≥ 55 years) (Breslow–Day test p value = 0.048), and the GA/GG genotype of the same SNP showed a borderline difference (Breslow–Day test p value = 0.051) (Table 5). We measured the layer-specific ORs in each age group using logistic regression. Compared with the AA genotype, GA and GA/GG genotypes were both associated with a significantly increased risk of GC in the people aged ≥ 55 years (OR = 1.60, 95% CI: 1.06–2.42, $p = 0.026$; OR = 1.51, 95% CI: 1.01–2.23, $p = 0.041$, respectively) but exhibited a decreased tendency of risk of GC in the people aged < 55 years (OR = 0.87, 95% CI: 0.56–1.35, $p = 0.528$; OR = 0.85, 95% CI: 0.56–1.29, $p = 0.444$, respectively). These results may suggest a modifying effect of age on *ALKBH1* rs1076496.

Determining the Optimal Genetic Model for Candidate SNPs

The genetic model represents the best-fitting manner in which an SNP influences the biology of a disease in population-based molecular association studies; therefore, determining the optimal genetic model for each candidate SNP by means of an appropriate method is crucial. For rs2287142, OR1, OR2, and OR3 were 0.77 ($p = 0.238$), 0.74 ($p = 0.003$), and 1.03 ($p = 0.893$), respectively, which was concordant with the principle represented by “OR1 = OR2 \neq 1 and OR3 = 1.” This data, therefore, fits well with a dominant model. For *ALKBH1* rs1076496 in people aged ≥ 55 years, OR1, OR2, and OR3 were 1.28 ($p = 0.350$), 1.60 ($p = 0.026$), and 0.80 ($p = 0.340$), respectively, which was also compatible with a dominant model (Table 6).

Haplotype Analysis

Figure 1 shows the statistical results of D' and r^2 used for evaluating LD between SNPs in *FTO* and *ALKBH1* genes. As Lauren classification is an important prognostic factor of GC, we also explored the influence of haplotypes on the risk conferred by each Lauren subtype of GC. When compared with the most common haplotype CTGT, the *FTO* rs1421091-rs1421092-rs2287142-rs9939609 CTAT haplotype showed a significant association with a lower total risk of GC (adjusted OR = 0.62, 95% CI: 0.41–0.93, $p = 0.023$), and the *FTO* CTGA haplotype was closely associated with an increased risk of intestinal GC (adjusted OR = 2.51, 95% CI: 1.32–4.76, $p = 0.005$) (Table 7).

Table 3 The Individual Genetic Effect of Candidate SNPs on the Risk of GC

SNP	Genotype	GC	Control	Crude Analysis		Adjusted Analysis	
				OR (95% CI)	p	OR (95% CI)	p
For FTO gene							
rs1421091	CC	173 (43.8%)	228 (42.5%)	1		1	
	CA	174 (44%)	244 (45.4%)	0.94 (0.71–1.24)	0.661	1.00 (0.75–1.33)	0.996
	AA	48 (12.2%)	65 (12.1%)	0.97 (0.64–1.48)	0.900	1.01 (0.66–1.56)	0.958
	CA/AA	222 (56.2%)	309 (57.5%)	0.95 (0.73–1.23)	0.683	1.00 (0.77–1.31)	0.982
	C	519 (66.1%)	700 (65.1%)	1		1	
rs1421092	A	265 (33.8%)	374 (34.8%)	0.96 (0.79–1.16)	0.646	0.96 (0.79–1.17)	0.711
	CC	109 (26.6%)	141 (25.4%)	1		1	
	TC	196 (47.8%)	293 (52.8%)	0.87 (0.64–1.18)	0.358	0.84 (0.61–1.15)	0.268
	TT	105 (25.6%)	121 (21.8%)	1.12 (0.78–1.61)	0.531	1.05 (0.72–1.51)	0.794
	TC/TT	301 (73.4%)	414 (74.6%)	0.94 (0.70–1.26)	0.679	0.90 (0.67–1.21)	0.494
rs2287142	T	405(50.0%)	535 (48.1%)	1		1	
	C	405 (50.0%)	575 (51.8%)	1.074 (0.90–1.29)	0.435	0.93 (0.78–1.12)	0.462
	GG	202 (51%)	242 (43.8%)	1		1	
	AG	155 (39.1%)	250 (45.2%)	0.74 (0.56–0.98)	0.033	0.73 (0.55–0.96)	0.025
	AA	39 (9.8%)	61 (11%)	0.77 (0.49–1.19)	0.237	0.75 (0.48–1.17)	0.217
rs9939609	AG/AA	194 (49%)	311 (56.2%)	0.75 (0.58–0.97)	0.027	0.73 (0.56–0.95)	0.020
	G	549 (69.6%)	734 (66.3%)	1		1	
	A	239 (30.3%)	372 (33.6%)	0.86 (0.70–1.05)	0.129	0.86 (0.71–1.05)	0.134
	TT	302 (73.7%)	420 (75.8%)	1		1	
	TA	102 (24.9%)	129 (23.3%)	1.10 (0.82–1.48)	0.533	1.11 (0.82–1.50)	0.504
rs1076496	AA	6 (1.5%)	5 (0.9%)	1.67 (0.50–5.52)	0.396	1.48 (0.44–4.96)	0.535
	TA/AA	108 (26.3%)	134 (24.2%)	1.12 (0.84–1.50)	0.446	1.13 (0.83–1.52)	0.440
	T	702 (86.2%)	969 (87.4%)	1		1	
	A	112 (13.7%)	139 (12.5%)	1.112 (0.85–1.45)	0.435	1.09(0.82–1.44)	0.553
	For ALKBH1 gene						
rs1048147	CC	184 (45.7%)	270 (49.1%)	1		1	
	AC	177 (43.9%)	233 (42.4%)	1.11 (0.85–1.46)	0.432	1.13 (0.86–1.48)	0.383
	AA	42 (10.4%)	47 (8.6%)	1.31 (0.83–2.07)	0.244	1.35 (0.85–2.14)	0.203
	AC/AA	219 (54.3%)	280 (50.9%)	1.15 (0.89–1.48)	0.294	1.17 (0.90–1.52)	0.247
	C	539 (67.8%)	773 (70.2%)	1		1	
rs1076496	A	255 (32.1%)	327 (29.7%)	1.12 (0.92–1.36)	0.266	1.12 (0.91–1.36)	0.288
	AA	109 (26.2%)	166 (29.6%)	1		1	
	GA	228 (54.8%)	279 (49.8%)	1.24 (0.92–1.68)	0.150	1.21 (0.89–1.63)	0.230
	GG	79 (19%)	115 (20.5%)	1.05 (0.72–1.52)	0.813	1.03 (0.71–1.51)	0.871
	GA/GG	307 (73.8%)	394 (70.4%)	1.19 (0.89–1.58)	0.237	1.16 (0.87–1.54)	0.323
rs11159286	A	441 (53.5%)	611 (54.5%)	1		1	
	G	383 (46.4%)	509 (45.4%)	1.04 (0.87–1.25)	0.651	1.05 (0.87–1.26)	0.629
	CC	266 (64.6%)	345 (62.2%)	1		1	
	CA	135 (32.8%)	185 (33.3%)	0.95 (0.72–1.24)	0.693	0.96 (0.73–1.27)	0.762
	AA	11 (2.7%)	25 (4.5%)	0.57 (0.28–1.18)	0.126	0.60 (0.29–1.26)	0.178
rs11159286	CA/AA	146 (35.4%)	210 (37.8%)	0.90 (0.69–1.18)	0.444	0.92 (0.70–1.20)	0.529
	C	663 (81.0%)	875 (78.8%)	1		1	
	A	155 (18.9%)	235 (21.1%)	0.87 (0.69–1.09)	0.229	0.88 (0.70–1.11)	0.281

Note: Analyses results with $p < 0.05$ were highlighted in bold characters.

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

Haplotypes of *ALKBH1* were also explored in different age groups as *ALKBH1* rs1076496 AA exhibited a connection with a lower risk of GC in the people aged ≥ 55 years. Consistent with these results, the *ALKBH1* rs1048147-rs1076496-rs11159286 CAC haplotype was significantly associated with a decreased risk of GC in people aged ≥ 55 years (adjusted

Table 4 The Modification Effect of Sex on the Associations of Candidate SNPs with GC Risk

SNP	Genotype	OR (95% CI)		p ^a
		For Male	For Female	
For <i>FTO</i> gene				
rs1421091	CC	1	1	
	CA	0.90 (0.66–1.23)	1.14 (0.64–2.03)	0.482
	AA	1.11 (0.69–1.78)	0.57 (0.21–1.52)	0.228
	CA/AA	0.94 (0.70–1.27)	0.99 (0.58–1.72)	0.862
rs1421092	CC	1	1	
	TC	0.86 (0.60–1.21)	0.88 (0.45–1.72)	0.939
	TT	1.20 (0.80–1.80)	0.90 (0.41–1.98)	0.530
	TC/TT	0.96 (0.69–1.32)	0.89 (0.47–1.68)	0.841
rs2287142	GG	1	1	
	AG	0.74 (0.54–1.01)	0.77 (0.44–1.35)	0.909
	AA	0.89 (0.54–1.47)	0.46 (0.18–1.20)	0.229
	AG/AA	0.77 (0.57–1.03)	0.69 (0.41–1.18)	0.747
rs9939609	TT	1	1	
	TA	1.08 (0.76–1.52)	1.18 (0.65–2.14)	0.797
	AA	3.44 (0.66–17.90)	0.48 (0.05–4.71)	0.151
	TA/AA	1.12 (0.80–1.58)	1.12 (0.62–2.01)	0.990
For <i>ALKBH1</i> gene				
rs1048147	CC	1	1	
	AC	1.17 (0.86–1.59)	0.96 (0.54–1.70)	0.549
	AA	1.57 (0.91–2.72)	0.85 (0.36–1.98)	0.229
	AC/AA	1.23 (0.91–1.65)	0.93 (0.55–1.58)	0.373
rs1076496	AA	1	1	
	GA	1.24 (0.88–1.73)	1.29 (0.68–2.45)	0.907
	GG	0.92 (0.60–1.42)	1.51 (0.70–3.25)	0.273
	GA/GG	1.14 (0.83–1.58)	1.35 (0.73–2.49)	0.634
rs11159286	CC	1	1	
	CA	0.95 (0.70–1.30)	0.94 (0.53–1.66)	0.971
	AA	0.49 (0.21–1.13)	0.98 (0.21–4.55)	0.432
	CA/AA	0.89 (0.66–1.20)	0.94 (0.54–1.64)	0.862

Notes: ^ap values for Breslow–Day test to compare the ORs of different sex groups.

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

OR = 0.41, 95% CI: 0.21–0.79, $p = 0.008$) (Table 8). *ALKBHI* haplotypes had no significant effect on the risk of total GC (Table 8) or GC defined by any Lauren classification (Table S3).

Cooperative Effect of SNPs Within *FTO* Haplotypes

A comparison of the *FTO* haplotypes CTAT and CTGA, which had opposite effects on the risk of GC, revealed that the variants at rs1421091 and rs1421092 were both CT, while the variants at rs2287142 and rs9939609 were different, suggesting that the variant combination at rs2287142 and rs9939609 was the crucial factor. In the subsequent analysis, we compared the risk of GC conferred by rs2287142 and rs9939609 genotype combinations with the remaining genotypes pooled as the reference and found that people simultaneously carrying rs2287142 AG/AA and rs9939609 TT had a markedly decreased risk of GC (adjusted OR = 0.71, 95% CI: 0.54–0.92, $p = 0.011$) (Table 9). The analysis of SNP combinations showed evidence of cooperative effects between the rs2287142 and rs9939609 sites on the *FTO* gene.

Two other *FTO* haplotypes, ACAT and CCAT, that also contained the AT variant of rs2287142-rs9939609, were not closely related with the risk of GC (Table 7). Unlike the GC-associated haplotype CTAT, the alleles at rs1421092 for these two haplotypes were C but not T. It was further observed that the AG/AA-TT combination of rs2287142 and rs9939609 was significantly associated with a decreased risk of GC only in the rs1421092 TC/TT group (adjusted OR =

Table 5 The Modification Effect of Age on the Associations of Candidate SNPs with GC Risk

SNP	Genotype	OR (95% CI)		p ^a
		Age < 55	Age ≥ 55	
For FTO gene				
rs1421091	CC	I	I	
	CA	1.19 (0.78–1.83)	0.90 (0.62–1.32)	0.340
	AA	1.23 (0.65–2.31)	0.91 (0.51–1.63)	0.496
	CA/AA	1.20 (0.80–1.80)	0.90 (0.63–1.29)	0.307
rs1421092	CC	I	I	
	TC	0.92 (0.58–1.45)	0.76 (0.49–1.17)	0.552
	TT	1.07 (0.61–1.87)	1.00 (0.61–1.64)	0.857
	TC/TT	0.96 (0.63–1.47)	0.83 (0.55–1.26)	0.641
rs2287142	GG	I	I	
	AG	0.54 (0.35–0.83)	0.93 (0.64–1.35)	0.059
	AA	0.97 (0.51–1.83)	0.63 (0.34–1.17)	0.339
	AG/AA	0.62 (0.42–0.92)	0.87 (0.61–1.23)	0.209
rs9939609	TT	I	I	
	TA	1.41 (0.90–2.20)	0.91 (0.61–1.38)	0.160
	AA	677577379.01 (677577379.01–677577379.01)	0.57 (0.13–2.40)	0.012
	TA/AA	1.51 (0.97–2.34)	0.89 (0.59–1.32)	0.080
For ALKBH1 gene				
rs1048147	CC	I	I	
	AC	1.08 (0.71–1.64)	1.17 (0.81–1.69)	0.785
	AA	1.81 (0.93–3.50)	1.03 (0.55–1.94)	0.229
	AC/AA	1.20 (0.81–1.77)	1.15 (0.81–1.62)	0.870
rs1076496	AA	I	I	
	GA	0.87 (0.56–1.35)	1.60 (1.06–2.42)	0.048
	GG	0.81 (0.46–1.41)	1.28 (0.76–2.15)	0.235
	GA/GG	0.85 (0.56–1.29)	1.51 (1.01–2.23)	0.051
rs11159286	CC	I	I	
	CA	1.06 (0.70–1.60)	0.89 (0.61–1.30)	0.540
	AA	0.52 (0.17–1.61)	0.66 (0.24–1.76)	0.762
	CA/AA	0.99 (0.66–1.48)	0.87 (0.60–1.25)	0.626

Notes: ^a*p* values for Breslow–Day test to compare the ORs of different age groups. Analyses results with *p* < 0.05 were highlighted in bold characters.

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

Table 6 The Optimal Genetic Model for Candidate SNPs

Gene_SNP	Comparison	GC versus Control	
		OR (95% CI)	<i>p</i>
<i>FTO</i> _rs2287142	AA versus GG (OR1)	0.77 (0.49–1.19)	0.238
	AG versus GG (OR2)	0.74 (0.56–0.98)	0.033
	AA versus AG (OR3)	1.03 (0.66–1.62)	0.893
	Dominant model		
<i>ALKBH1</i> _rs1076496 ^a	AG/AA versus GG	0.75 (0.58–0.97)	0.027
	GG versus AA (OR1)	1.28 (0.76–2.15)	0.350
	GA versus AA (OR2)	1.60 (1.06–2.42)	0.026
	GG versus GA (OR3)	0.80 (0.51–1.26)	0.340
	Dominant model		
	GA/GG versus AA	1.51 (1.02–2.23)	0.042

Note: ^aThe OR1–3 for *ALKBH1* rs1076496 were explored in people ≥55 years. Analyses results with *p* < 0.05 were highlighted in bold characters.

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

	ALKBH1			FTO			
	rs1048147	rs1076496	rs11159286	rs1421091	rs1421092	rs2287142	rs9939609
D' statistic							
ALKBH1_rs1048147		0.9462	0.9844				
ALKBH1_rs1076496			0.9994				
ALKBH1_rs11159286							
FTO_rs1421091				0.9810	0.0211	0.2023	
FTO_rs1421092					0.1102	0.2030	
FTO_rs2287142						0.5514	
FTO_rs9939609							
r²							
ALKBH1_rs1048147		0.3383	0.1099				
ALKBH1_rs1076496			0.2150				
ALKBH1_rs11159286							
FTO_rs1421091				0.4833	0.0004	0.0033	
FTO_rs1421092					0.0054	0.0065	
FTO_rs2287142						0.0215	
FTO_rs9939609							

Figure 1 The D' and r² for linkage disequilibrium evaluation of *FTO* SNPs and *ALKBH1* SNPs.

0.70, 95% CI: 0.49–0.99, *p* = 0.047) but not in the rs1421092 CC group (adjusted OR = 0.77, 95% CI: 0.30–2.00, *p* = 0.592). These results led us to distinguishing three loci on *FTO* that might share biological mechanisms in GC.

Discussion

In this study, we genotyped seven potentially functional SNPs of *FTO* and *ALKBH1* using the DNA samples collected from 419 patients with GC and 569 healthy controls. According to our results, the *FTO* rs2287142 AG and AG/AA variants were stably associated with a reduced risk of GC, regardless of sex and age. This SNP was predicted to be an exonic splicing enhancer/silencer, a type of splicing regulatory *cis*-element that can recruit *trans*-acting factors and determine splicing sites, thus possibly generating functionally different isoforms.²⁶ Therefore, we speculated that *FTO* rs2287142 might affect susceptibility to GC by modulating *FTO* splicing, which might produce transcripts that differ in function or quantity.

SNPs, together with certain features of a particular population, are known to affect the risk of cancer. For instance, rs298982 GA/AA of *METTL14* encoding an m6A methyltransferase exerts a protective effect against acute lymphoblastic leukemia only in children aged < 10 years and in males.²⁷ Similarly, we found that the GA and GA/GG genotypes of *ALKBH1* rs1076496 were closely associated with a higher risk of GC in people aged ≥ 55 years, but showed a decreasing tendency of risk of GC in people aged < 55 years. The rs9939609 AA showed a significant *p* value for the Breslow–Day test, possibly due to the small sample size of this group (Table 5), which was confirmed by subsequent analysis that revealed a negative result. In addition to sex and age, the Lauren classification is another common stratification factor that has been widely accepted as an independent prognostic indicator of GC.²⁸ The *FTO* CTGA haplotype was linked with an increased risk of intestinal GC, but not with that of mixed or diffuse GC, suggesting that this haplotype might only exert a genetic effect on certain histological subtypes of GC.

Haplotypes tend to have enhanced power of predicting disease-related genes compared to that of single SNPs.²³ CTAT carriers of the *FTO* haplotype rs1421091-rs1421092-rs2287142-rs9939609 had an OR showing a significantly lower susceptibility to GC (adjusted OR = 0.62), which was lower than the OR of carriers with the single SNP rs2287142 (adjusted OR = 0.73). The *ALKBH1* CAC haplotype was associated with a lower OR for the risk of GC (adjusted OR = 0.41) than that of the single rs1076496 variant AA (adjusted OR = 0.56) in people aged ≥ 55 years. Within the *FTO*

Table 7 The Influence of *FTO* Haplotypes on the Risk of Total GC and GC of Each Lauren's Classification

<i>FTO</i> Haplotype	Control (N=569)	Total GC (N=419)			Mixed Type (N=116)			Diffuse Type (N=151)			Intestinal Type (N=128)		
		Cancer	OR (95% CI)	<i>p</i>	Cancer	OR (95% CI)	<i>p</i>	Cancer	OR (95% CI)	<i>p</i>	Cancer	OR (95% CI)	<i>p</i>
CTGT	26.2%	29.5%	1		26.2%	1		31.8%	1		28.7%	1	
ACGT	19.8%	20.7%	1.05 (0.76–1.45)	0.762	22.1%	1.35 (0.77–2.36)	0.291	21.4%	0.94 (0.60–1.47)	0.790	19.2%	1.04 (0.64–1.68)	0.872
CTAT	15.8%	10.1%	0.62 (0.41–0.93)	0.023	9.8%	0.88 (0.43–1.76)	0.712	10.3%	0.56 (0.30–1.05)	0.072	11.1%	0.81 (0.44–1.48)	0.493
ACAT	10.8%	10.8%	0.96 (0.66–1.39)	0.810	12.3%	1.13 (0.61–2.10)	0.690	9.7%	0.79 (0.45–1.38)	0.402	10.3%	0.97 (0.55–1.72)	0.912
CCGT	9.4%	8.8%	0.97 (0.63–1.50)	0.900	6.6%	0.83 (0.38–1.79)	0.633	10.2%	1.06 (0.61–1.82)	0.841	8.9%	1.14 (0.59–2.18)	0.704
CTGA	6.0%	8.2%	1.40 (0.85–2.32)	0.192	7.2%	1.58 (0.72–3.49)	0.254	5.4%	0.89 (0.43–1.85)	0.763	12.7%	2.51 (1.32–4.76)	0.005
CCAT	5.5%	6.0%	0.97 (0.57–1.63)	0.901	6.9%	1.25 (0.59–2.66)	0.561	5.0%	0.66 (0.30–1.44)	0.305	6.0%	0.96 (0.45–2.04)	0.910
ACGA	3.3%	2.1%	0.61 (0.26–1.40)	0.240	5.2%	1.67 (0.66–4.20)	0.280	0.7%	0.25 (0.06–1.10)	0.067	0.0%	0.00 (-Inf-Inf)	1.000

Note: All analyses were adjusted by sex and age. The results highlighted in bold show significant associations with GC (*p* values <0.05).

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

Table 8 The Associations of *ALKBH1* Haplotypes with the Risk of Total GC and GC of Different Age Group

<i>ALKBH1</i> Haplotype	Control (N=569)	Total GC (N=419)			Age < 55 (N=159)			Age ≥ 55 (N=260)		
		Cancer	OR (95% CI)	p	Cancer	OR (95% CI)	p	Cancer	OR (95% CI)	p
CGC	44.9%	45.1%	1		41.9%	1		47.2%	1	
AAC	28.4%	30.9%	1.09 (0.88–1.35)	0.441	33.2%	1.15 (0.78–1.70)	0.49	29.5%	0.87 (0.63–1.19)	0.380
CAA	21.2%	19.2%	0.90 (0.70–1.16)	0.410	20.3%	0.98 (0.63–1.52)	0.92	18.3%	0.73 (0.50–1.05)	0.088
CAC	4.7%	3.7%	0.71 (0.44–1.16)	0.172	3.6%	1.43 (0.60–3.39)	0.42	3.7%	0.41 (0.21–0.79)	0.008

Notes: All analyses were adjusted by sex and age. The results highlighted in bold show significant associations with GC (*p* values <0.05).

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

Table 9 The Cooperation Effect of *FTO* rs2287142 and rs9939609 on GC Risk

rs2287142	rs9939609	Genotype Combination	Cancer	Control	OR (95% CI)	p
AG/AA	TA/AA	AG/AA-TA/AA	47 (11.2%)	57 (10.0%)	1.11 (0.73–1.70)	0.623
AG/AA	TT	AG/AA-TT	150 (35.8%)	250 (43.9%)	0.71 (0.54–0.92)	0.011
GG	TA/AA	GG-TA/AA	61 (14.6%)	77 (13.5%)	1.11 (0.77–1.61)	0.572
GG	TT	GG-TT	136 (32.5%)	157 (27.6%)	1.28 (0.97–1.70)	0.082

Notes: All analyses were adjusted by sex and age. The results highlighted in bold show significant associations with GC (*p* values <0.05).

Abbreviations: CI, confidence interval; GC, gastric cancer; OR, odds ratio; SNP, single nucleotide polymorphism.

haplotype, rs1421092 TC/TT presentation was the prerequisite for the AG/AA-TT combination of rs2287142 and rs9939609 to influence the risk of GC. This emphasized the essential role of SNP-SNP interaction analysis, without which the cooperative effect of rs1421092, rs2287142 and rs9939609 would have not been detected.

FTO, also known as *ALKBH9*, belongs to the non-heme Fe II/ α -ketoglutarate-dependent dioxygenase *AlkB* family that also contains *ALKBH1*–*ALKBH8*.¹¹ *FTO* and *ALKBH1* have been established as important regulators of malignant phenotype and the therapeutic response of cancer cells.²⁹ Decreased *FTO* mRNA levels have been demonstrated to be associated with a poor prognosis in renal cell carcinoma,³⁰ and the silencing of *FTO* is considered to be associated with selective reduction of the in vitro and in vivo survival of von Hippel–Lindau-deficient renal carcinoma cells.³¹ The cytotoxicity induced by cisplatin in bladder cancer cells is known to be reverted by co-treatment with the *FTO* selective inhibitor MA2, an ethyl ester derivative of meclofenamic acid.³² *FTO* is also known to be related to tumor immune infiltration observed in various cancers.³³ With immunotherapy attracting extensive attention for treating multiple cancers, including advanced GC,³⁴ genetic variants may potentially serve as novel biomarkers for predicting immunological response. *ALKBH1* has been reported to be up-regulated in lung cancer. Silencing and overexpression of *ALKBH1* could, respectively, suppress and promote the invasion and migration of lung cancer cells.³⁵ As the change in expression of *FTO* or *ALKBH1* is relevant to cancer development, it could be speculated that SNPs localized at the key regulatory sites of *FTO* and *ALKBH1* might make a difference in cancer development, possibly by influencing the expression levels of the host genes.

FTO polymorphisms are known to affect risk and prognosis of cancers. *FTO* rs16953002 and rs12596638 have been reported to markedly influence melanoma susceptibility.³⁶ *FTO* rs7202116 has a statistically significant association with a shorter overall survival of patients with hepatocellular carcinoma treated with transhepatic arterial chemotherapy and embolization.³⁷ The *ALKBH1* SNP has not been extensively studied. The SNP rs3850370, which is 360 kb downstream of *ALKBH1*, has been reported to modulate the survival of non-small cell lung cancer across Chinese and Caucasian populations.²² Apart from *FTO* rs9939609, all the other SNPs researched in this study had not been previously explored in terms of their association with any disease. *FTO* rs9939609 variant A is a protective factor for lung cancer.³⁷ Our data showed the *FTO* haplotype rs1421091-rs1421092-rs2287142-rs9939609 CTGA to be linked to an increased susceptibility to intestinal GC, illustrating that the same allele of a SNP can play different roles in different cancer types.

This study, however, has some limitations to be acknowledged. The sample size could be increased to obtain more reliable results. Additionally, we could not analyze the relationship between the SNP genotypes and the expression levels

of FTO and ALKBH1 due to the unavailability of sufficient GC tissues. Moreover, the possibility of SNPs affecting the alternative splicing sites remained unexplored in this study. These limitations and the results warrant deeper research to help further understand the mechanisms behind the association of SNPs with GC in the future.

Conclusion

In summary, *FTO* rs2287142, individually or within a haplotype, notably decreased the risk of GC, whereas *ALKBH1* rs1076496 was closely associated with an increased risk of GC in the people aged ≥ 55 years. Our data shows that *FTO* and *ALKBH1* SNPs may have predictive value in evaluating susceptibility to GC with differing age or Lauren classification. Large-scale multicenter studies and functional experiments are needed in future to further validate these results.

Abbreviations

ALKBH1, alkB homolog 1; CI, confidence interval; ESE/ESS, exonic splicing enhancer/silencer; FTO, fat mass and obesity-associated protein; GC, gastric cancer; LD, linkage disequilibrium; m6A, N6-methyladenosine; OR, odds ratio; SNP, single nucleotide polymorphism; TFBS, transcriptional factor binding site.

Data Sharing Statement

The datasets used or analyzed in the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (Guangzhou, China) (approval NO. G2022-002-01). Written informed consent was provided by all participants at their first visit. All experiments were performed in accordance with the guidelines stated in the Declaration of Helsinki.

Consent for Publication

The purpose of this study was well informed to the all participants and written informed consent was obtained from the all participants for publication of this report.

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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

The authors report no conflicts of interest in this work.

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