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No association of the single nucleotide polymorphism rs8044769 in the fat mass and obesity-associated gene with knee osteoarthritis risk and body mass index

A POPULATION-BASED STUDY IN CHINA

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Objectives

Previous genome-wide association studies (GWAS) have reported significant association of the single nucleotide polymorphism (SNP) rs8044769 in the fat mass and obesity-associated gene (FTO) with osteoarthritis (OA) risk in European populations. However, these findings have not been confirmed in Chinese populations.

Methods

We systematically genotyped rs8044769 and evaluated the association between the genetic variants and OA risk in a case-controlled study including 196 OA cases and 442 controls in a northern Chinese population. Genotyping was performed using the Sequenom MassARRAY iPLEX platform.

Results

We found that the variant T allele of rs8044769 showed no significant association of OA risk ($p = 0.791$), or association with body mass index (BMI) ($p_{meta} = 0.786$) in an additive genetic model. However, we detected a significant interaction between rs8044769 genotypes and BMI on OA risk ($p = 0.037$), as well as a borderline interaction between rs8044769 genotypes and age on OA risk ($p = 0.062$).

Conclusions

Our findings indicate that rs8044769 in the FTO gene may not modify individual susceptibility to OA or increased BMI in the Chinese population. Further studies are warranted to validate and extend our findings.

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Keywords: OA; Susceptibility; rs8044769; FTO

Article focus

- To date,no previous study has been conducted to explore the possibility that the single nucleotide polymorphism (SNP) rs8044769 in the fat mass and obesity-associated (FTO) gene predisposes patients to osteoarthritis (OA) development in Asian populations. We investigated the association between the SNP rs8044769 in the FTO gene and osteoarthritis in the Chinese population.

Key messages

- The SNP rs8044769 in the FTO gene was not associated with OA risk in the Chinese population. Further studies are warranted to validate and extend our findings.

Strengths and limitations

- Strengths: This is the first report on the association between the SNP rs8044769 in FTO gene and OA diseases in the Chinese population. Our findings showed that SNP rs8044769 in the FTO gene may neither modify individual susceptibility to OA or increased body mass index in the Chinese population.
- Limitations: More studies should be conducted with larger sample sizes and using different ethnic groups to validate and extend our findings.

Introduction

Osteoarthritis (OA) is the most common degenerative joint disease and has emerged as a major public health concern around the world.[1-3] OA is predicted to be the single greatest cause of disability in the general population by 2030.[4] Similar increasing trends of OA prevalence can also be found in China.[5] Despite its high prevalence and substantial public health impact, the aetiology of OA is not fully understood. OA may be considered as a polygenic disease, which is the combined interaction of multiple factors including individual genetic origins and environmental components.[6] Epidemiological evidence suggests that ageing, genetic predisposition, obesity, inflammation and excessive mechanical loading predispose to OA development.[7-9] Furthermore, the identification of candidate genes and pathways would help elucidate the molecular mechanisms of OA, and have the potential to evaluate the risk for OA and lead to the development of OA gene-targeted therapies.[10]

Epidemiological studies have shown that OA has strong genetic components,[11-13] and a number of candidate genes have been implicated as susceptibility loci for primary OA, such as type II procollagen gene(COL2A1),[14] oestrogen receptor-α(ESR-α),[15] growth differentiation factor 5(GDF5),[16] double von Willebrand factor A domains (DVWA),[17] interleukin-6(IL-6),[18] the secreted frizzled-related protein (FRZB)[19,20] and Asporin.[21]

Recently, compelling evidence has suggested that obesity is one of the strongest predictive and prognostic factors for OA, particularly in knee joints, and is considered to be moderately associated with hip OA.[22-26] Previous genetic studies of the fat mass and obesity-associated gene (FTO) have principally focused on obesity properties, which are currently considered as the first and the most consistently replicated candidate genes contributing to obesity in multiple populations of different countries.[27-31] The FTO gene, located on chromosome 16q12.2, consists of nine exons and encodes a 2-oxoglutarate-dependent nucleic acid demethylase. FTO was discovered as an obesity susceptibility gene in 2007.[32] Subsequently, a cluster of variants of the FTO gene was identified as those carrying the association and predisposition to obesity-related traits in European populations in both adults and children.[27,33] However, these associations remain controversial. To date, more than 100 single nucleotide polymorphisms (SNPs) in the FTO gene have been reported, among which the rs8044769 is a well-established SNP that is associated with fat mass and obesity, and it is in partial linkage disequilibrium (LD) with other reported body mass index (BMI)(mass/height^2)-associated SNPs.[27] Interestingly, a recent large well powered genome-wide association study (GWAS) has identified the variant SNP rs8044769 as being strongly associated with risk of OA development.[34] However, the fact that the effect was thoroughly attenuated with adjustment for BMI indicates that the FTO gene may exert its effect on OA through obesity;[35] that is, the strong association between FTO and OA risk was mediated by BMI.

To the best of our knowledge, no previous study has been undertaken to explore the possibility that the SNP rs8044769 in FTO gene predisposes to OA development in Asian populations. The understanding of ethnicity-specific gene effects would be valuable for the human OA population. On this basis, we speculate that the SNP rs8044769 may influence the susceptibility to OA in the Asian population. We focused on one SNP of special interest: cytosine/thyamine (rs8044769) in the promoter region of the FTO gene. The current study tested the following two hypotheses in the Chinese population: that SNP rs8044769 is associated with susceptibility to OA and that SNPrs8044769 is associated with BMI.

Materials and Methods

Study population and study design. We performed a case-controlled study to evaluate whether the SNP rs8044769 was associated with knee OA in a Chinese population consisting of 196 cases and 442 controls from a community-based prospective study of knee OA in Harbin, a city of Heilongjiang Province, China (patients not matched). In this study, eligible subjects aged 40 and over were enrolled. Patients with primary OA in at least one knee joint were categorised into the case group, while those without knee OA were categorised into the control group. A questionnaire was designed to collect information from participants regarding general information, occupational and sports activities, previous knee injuries, family history of OA and other diseases, and clinical manifestations of OA. All study subjects underwent a physical examination, including anthropometric measurements.

OA patients were diagnosed by definite signs and symptoms of OA, including radiographic evidence of OA and at least one month of joint pain during the previous 12 months. For OA patients, radiographic findings were assessed using the Kellgren-Lawrence (K/L) grading system,(graded 0 to 4, where 0 = none; 1 = possible osteophytes only; 2 = definite osteophytes and possible joint space narrowing; 3 = moderate osteophytes and/or definite joint space narrowing; and 4 = large osteophytes, severe joint space narrowing, and/or bony sclerosis).[36] In the K/L grading system, radiographs were scored from grade 0 to grade 4, with the higher grades being associated with more severe OA. Knee OA on the radiographs was defined as K/L grade $\geqslant$ 2 for either knee joint. Lateral and anteroposterior knee radiographs were read independently by two radiologists (JR and SW) who were blinded to patient presentation. Discrepancies were resolved by consensus. Any radiographs on which a consensus could not be reached were re-examined by a specialist (TT) to ensure thier validity. Those who had no signs or symptoms of arthritis or joint diseases were diagnosed as healthy subjects. In addition, secondary OA patients such as those with inflammatory or rheumatoid

Table I. Distributions of select variables in osteoarthritis cases and controls

Variables	Cases (n = 196)	Controls (n = 442)	p-value
Age, (yrs) (mean, SD)	62.19 SD 8.76	57.17 SD 9.19	< 0.001
	n (%)	**n (%)**	
< 57*	56 (*29*)	213 (*48*)	< 0.001
⩾ 57*	140 (*71*)	229 (*52*)	
Gender			
Male	48 (*24*)	139 (*31*)	0.090
Female	148 (*76*)	303 (*69*)	
Body mass index			
Underweight (< 19.5)	4 (*2*)	22 (*5*)	
Normal (19.5 to 24.9)	79 (*40*)	237 (*54*)	
Overweight (25.0 to 29.9)	93 (*47*)	145 (*33*)	0.006
Obese I (30.0 to 34.9)	16 (*8*)	33 (*7*)	
Obese II (35.0 to 39.9)	3 (*2*)	4 (*1*)	
Obese III (> 40.0)	1 (*1*)	1 (*0*)	
Smoking status			
Ever	46 (*23*)	119 (*27*)	0.330
Never	150 (*77*)	318 (*73*)	
Drinking status			
Ever	52 (*28*)	134 (*33*)	0.254
Never	135 (*72*)	277 (*67*)	

*Median age in control group.
SD, standard deviation.

Table II. Association between the single nucleotide polymorphism rs8044769 and osteoarthritis risk in a logistic regression model

Genotype	Cases (%)	Controls (%)	OR (95% confidence interval)†	p-value†
SNP rs8044769 (C>T)*				
CC	72 (*37.31*)	167 (*38.30*)	1	
CT	89 (*46.11*)	194 (*44.50*)	1.19 (0.80 to 1.76)	0.386
TT	32 (*16.58*)	75 (*17.20*)	1.00 (0.60 to 1.69)	0.988
Dominant			1.13 (0.79 to 1.64)	0.500
Additive			1.03 (0.81 to 1.32)	0.791

*Major allele > Minor allele
†Logistic regression with adjustment for age, gender and body mass index

arthritis, bone fracture and developmental dysplasia were excluded.

BMI is the most widely used anthropometric measure of weight status. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass was measured with a digital scale to the nearest 0.1 kg. The classification of obesity status was defined according to the World Health Organization's definition: Underweight (BMI < 19.5), Normal (BMI 19.5 to 24.9), Overweight (BMI 25.0 to 29.9), Obese I (BMI 30.0 to 34.9), Obese II (BMI 35.0 to 39.9), Obese III (BMI > 40.0).

The protocols for sample collection, sample anonymity, storage and genomic DNA analysis were approved by the Institutional Review Board for the Ethics Committee for Human Genome Analysis at Harbin Medical University, Harbin, China. Written informed consent from all the participants was obtained. The clinical study was conducted according to the Declaration of Helsinki principles.

Genotyping. Peripheral blood was collected from each subject only after obtaining signed informed consent, and genomic DNA was extracted from the samples by a DNA Extraction Kit (Qiagen Inc., Valencia, California). Genotyping analysis was performed using the Sequenom MassARRAY iPLEX platform (Sequenom Inc., San Diego, California), which can genotype more than 20 SNPs in each well. The following series of methods were used to control the quality of genotyping: case and control samples were mixed on each plate; genotyping was performed blinded to case or control status; two water controls were used in each plate as blank controls; and 5% of the samples were randomly selected for repeat genotyping, as blind duplicates, and the reproducibility was 100%.

Statistical analysis. The chi-squared test for categorical variables and Student's *t*-test for continuous variables were used to analyse distribution differences of demographic characteristics, selected variables and genotypes between cases and controls. The Hardy-Weinberg equilibrium (HWE) for the distribution of each SNP was evaluated using the chi-square goodness of fit test by comparing the observed genotype frequencies with the expected ones among the controls. Odds ratios (ORs) and their 95% confidence intervals (CI) were calculated by using logistic regression analyses to evaluate the association between SNPs and OA risk with an adjustment for age, gender and BMI. The BMI values were normalised by log transformation for multiple linear regressions to assess the association between SNP rs8044769 and BMI with an adjustment for age and gender. The β parameter means there was an expected change in BMI for a one-unit change of the SNP. In order to examine the differences between subgroups, the chi-square based Cochran's Q-test was used to test the heterogeneity of effect sizes (ORs and 95% CIs) derived from corresponding subgroups. All of the statistical analyses were performed with Stata Version 12.0 software (StataCorp LP, College Station, Texas).

Results

The distribution of selected characteristics between the 196 OA cases and the 442 controls are summarised in Table I. In brief, the gender distribution between cases and controls was comparable (p >0.05). The mean age of the cases was higher than that of the controls. Compared with controls, the cases had a higher rate of an overweight BMI (47% *vs* 33%).The smoking and drinking status between cases and controls could be compared (p > 0.05).

The basic information on the SNP rs8044769is shown in the supplementary material (Table i).The success rate for genotyping for this polymorphism is 98.59% in the current study. The observed genotype frequency for the SNP rs8044769 was in agreement with HWE in the controls (p = 0.15). As shown in Table II, the variant T allele showed no significant association for OA risk in all tested models (CT *versus* CC: OR = 1.19, 95% CI 0.80 to 1.76; TT *versus* CC: OR = 1.00, 95% CI 0.60 to 1.69; dominant

Table III. Association between the single nucleotide polymorphism rs8044769 and body mass index in multiple linear regression model

Group	Subjects	β (95%confidence interval)*	p*	p_{het}†
Osteoarthritis cases	196	0.001 (–0.011 to 0.013)	0.882	
Osteoarthritis controls	442	0.003 (–0.005 to 0.011)	0.479	
Meta-analysis		0.002 (–0.004 to 0.009)	0.483	0.786

*Data were analysed under an additive genetic model and adjusted for age and gender
†*P* for heterogeneity

model: OR = 1.13, 95% CI 0.79 to 1.64; additive model: OR = 1.03, 95% CI 0.81 to 1.32).

Furthermore, in the stratification analysis, the association between the SNP rs8044769 and OA risk was evaluated in subgroups based on age, gender, BMI, smoking status and drinking status. As shown in the supplementary material (Table ii), no significant difference between any subgroups was observed for the association between the SNP rs8044769and OA risk.

Because obesity and age are both established risk factors for OA, we further investigated whether the effect of the SNP rs8044769 variant on OA was modified by age and BMI. As shown in Supplementary Table iii, the interaction of the SNP rs8044769 and age had a borderline significant association with OA risk (interaction p=0.062). Individuals over 57 years old, as well as those carrying the CT/TT genotype had a 149% increased risk of developing OA (OR = 2.49, 95% CI 1.37 to 4.52) compared with those under 57 years old carrying the CC genotype. A similar interactive effect was observed between the SNPrs8044769variant and BMI contributing to the risk for OA (interaction p =0.037) (Supplementary Table iv).

Out of interest, we also investigated whether the SNP rs8044769 is associated with BMI in our study cases and controls, respectively. As shown in Table III, the SNP rs8044769showed no significant association with BMI in the OA case group (p = 0.882 in additive model), while a similar result was observed in the OA control group (p = 0.479 in additive model). Not surprisingly, further meta-analysis of the results from the two groups indicated that the SNP rs8044769 shows no significant association with BMI (p_{meta}=0.483).

Discussion

Genetic polymorphisms are involved in biodiversity and could be influenced by ethnic heritage and geographic localisation.[37] It is therefore of interest to explore the geographical and ethnic distribution of genetic polymorphisms. The purpose of this study was to examine the FTOSNP rs8044769 as a potential genetic candidate for knee OA by means of an association study in a Chinese population. We evaluated the association of the SNP rs8044769with OA risk in a case-control study including 196 cases and 442 controls in a northern Chinese population. The variant T allele of the SNP rs8044769 showed no significant association with OA risk. In addition, the SNP rs8044769 showed no significant association with BMI. To the best of our knowledge, this is the first association study of polymorphisms in FTO with OA and BMI in the Chinese population. Although our association findings are negative, replication in larger studies should be considered given the possibility of beta error due to population stratification and small sample size.

Our present study showed no significant association between the FTOSNP rs8044769polymorphism and OA risk. However, in previous studies conducted in the European population, the SNP rs8044769was definitively associated with increased OA risk.[38] There are several reasons for this discrepancy. First, the difference may be due to genetic heterogeneity between different ethnicities since the allele frequency of the SNP rs8044769 polymorphism displays differences among the Asian and European populations.[38] Secondly, the sample size of our population might not be large enough to reach a convincing conclusion. Thirdly, bias in patient enrolment criteria and differences in OA affected joint sites could also confound study findings.

The present study has several strengths. First, our OA cases came from a systematic screening of OA in a large population-based study conducted in Heilongjiang Province, while the controls also came from the same *community*, which may have reduced potential selection bias. Secondly, OA phenotypic definitions, which reflect a different subset of OA, have been shown to influence the ability to detect genetic associations. The focus on radiographic features and clinical diagnosis in the definition of OA is a strength because analyses of patients identified by more stringent and clinically relevant criteria have more powerful implications. Thirdly, by exerting much effort in identifying whether the SNP rs8044769 is associated with BMI, we performed analyses on the OA case group and the OA control group, respectively, and further combined the results using a meta-analysis. Thus, our strictly designed analyses were likely to produce reliable results. Additionally, with effort to maximise the success and accuracy rates of genotyping, we used the Sequenom genotyping platform with stringent quality controls.

However, several limitations of our study also need to be addressed. First, OA is a multifactorial disease with a strong genetic component with various heritability estimates depending on different joint sites. We only evaluated the risk of knee OA and the SNP rs8044769 in the FTO gene and the results cannot be generalised to OA in other joints. Secondly, the current sample size (196 OA

cases and 442 control subjects) has a statistical power of 46.55% to detect an effect size of 1.50 with an α-level of 0.05 for the association of the SNP rs8044769 with OA risk. Thus, well-conducted larger sample studies are needed to explore further the OA risk associated withthe SNP rs8044769in Chinese populations. Thirdly, we only genotyped the previously-reported SNP rs8044769 in FTO. Further studies are required in order to genotype more SNPs in FTO, and evaluate whether other SNPs in FTO are associated with OA, as well as BMI, in Chinese populations.

In conclusion, our study investigated the role of the SNP rs8044769 in the FTO gene in OA development and BMI in a Chinese population. The results of our study draw attention to one important issue: the SNP rs8044769presentsno distinct association with OA or BMI in a northern Chinese population. The result is different from the recent GWAS study on hip and/or knee OA.[39] Replication of FTO association in other larger study samples is essential for clarification as OA merits significant attention in order to develop better prevention strategies and therapies that can be applied globally. Given the fact that genetic factors may vary with different disease patterns, severity, gender and populations, studies in larger and more diverse populations are warranted.

Supplementary material

Tables showing a summary of the SNP rs8044769, stratified analysis of the association between the SNP rs8044769 and OA risk, the interaction between the SNP rs8044769 genotypes and age on OA risk, and the interaction between the SNP rs8044769 genotypes and BMI on OA risk are available alongside the online version of this article at www.bjr.boneandjoint.org.uk.

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Author Contribution
- Y. Wang: Data collection and analysis.
- M. Chu: Study design and writing the paper.
- J. Rong: Performed surgeries.
- B. Xing: Data collection and analysis.
- L. Zhu: Data collection and analysis.
- Y. Zhao: Data collection and analysis.
- X. Zhuang: Study design.
- L. Jiang: Study design and writing the paper.

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ICMJE conflict of interest
- None declared.