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EXTENDED REPORT

The effect of *FTO* variation on increased osteoarthritis risk is mediated through body mass index: a mendelian randomisation study

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ABSTRACT

Objective Variation in the fat mass and obesity-associated (*FTO*) gene influences susceptibility to obesity. A variant in the *FTO* gene has been implicated in genetic risk to osteoarthritis (OA). We examined the role of the *FTO* polymorphism rs8044769 in risk of knee and hip OA in cases and controls incorporating body mass index (BMI) information.

Methods 5409 knee OA patients, 4355 hip OA patients and up to 5362 healthy controls from 7 independent cohorts from the UK and Australia were genotyped for rs8044769. The association of the *FTO* variant with OA was investigated in case/control analyses with and without BMI adjustment and in analyses matched for BMI category. A mendelian randomisation approach was employed using the *FTO* variant as the instrumental variable to evaluate the role of overweight on OA.

Results In the meta-analysis of all overweight (BMI≥25) samples versus normal-weight controls irrespective of OA status the association of rs8044769 with overweight is highly significant (OR[CIs] for allele G=1.14 [01.08 to 1.19], $p=7.5\times10^{-7}$). A significant association with knee OA is present in the analysis without BMI adjustment (OR[CIs]=1.08[1.02 to 1.14], p=0.009) but the signal fully attenuates after BMI adjustment (OR[CIs]=0.99[0.93 to 1.05], p=0.666). We observe no evidence for association in the BMI-matched meta-analyses. Using mendelian randomisation approaches we confirm the causal role of overweight on OA.

Conclusions Our data highlight the contribution of genetic risk to overweight in defining risk to OA but the association is exclusively mediated by the effect on BMI. This is consistent with what is known of the biology of the *FTO* gene and supports the causative role of high BMI in OA.

INTRODUCTION

Osteoarthritis (OA) is the most common articular disease in the developed world and a leading cause of chronic disability, mostly as a consequence of knee OA and/or hip OA.[1] A number of studies have shown that obesity represents one of the most important risk factors and it is also a predictor for progression of OA, especially of the knee joint and less of the hip joint. There is a strong and highly significant relationship between body mass index (BMI) and OA of the knee. The relationship with hip OA is less striking but is still highly statistically significant[2 3] and obesity is one of the strongest prognostic factors for large joint OA.[4]

Genome-wide association studies (GWAS), which test the correlation between single-nucleotide polymorphisms (SNPs) across the entire genome and trait variation in a sample of individuals, have succeeded in identifying variants associated reproducibly with complex traits. The association between *FTO* SNPs and BMI and the risk of being overweight or obese has been confirmed in multiple populations.[5] The effect of *FTO* SNPs on BMI is modest, with those individuals homozygous for the risk allele weighing, on average, 3 kg more than those homozygous for the protective allele.[6]

The protein encoded by *FTO* has been described as a Fe(II)-oxoglutarate-dependent oxygenase and 2-oxoglutarate-dependent oxygenase that might operate as a DNA demethylase. The human *FTO* gene is expressed in many tissues including mesenteric fat, pancreas, liver and adipose tissue, with the highest concentrations found in the hypothalamus.[7] Experimental animal studies provide direct functional evidence that *FTO* underlies obesity.[8] Two studies have demonstrated that *FTO* gene expression in the arcuate nucleus of the hypothalamus is regulated by fasting,[9 10] suggesting that *FTO* may be important to the control of energy homeostasis.

A recent GWAS on hip and/or knee OA has identified a variant in the *FTO* gene, rs8044769, as being strongly associated with risk of OA.[11] Because of the study design, the authors were not able to test thoroughly whether the association between *FTO* and OA was mediated by obesity or not. GWAS for type 2 diabetes (T2D) detected strong association between common SNPs in the *FTO* region and risk of T2D.[6 12 13] However, subsequent analyses showed that the association between *FTO* SNPs and T2D was mediated by an association with BMI.[6]

There has been a lot of debate in the literature recently about the role of *FTO* in OA pathogenesis and specifically about the direction of causation between obesity and OA.[14 15] Mendelian randomisation, a form of instrumental variable analysis, is a

method of using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease in non-experimental studies.[16] The main elements for it to work (having removed the effect of confounders) are that the genetic variant should be reliably associated with the exposure, in this case overweight status, and that there should be no direct effect of genotype on disease or any other mediated effect other than through the exposure of interest. In our study we find that these conditions apply to the relationship between *FTO*, overweight and OA.

The aim of the present study is to elucidate the role of rs8044769 in genetic risk of OA by testing this SNP in seven independent study cohorts from the UK and Australia with BMI information comprising in total 5409 knee OA patients, 4355 hip OA patients and 5362 healthy individuals. We explore the causality and direction of the relationship between overweight status and OA using the *FTO* polymorphism as the instrumental variable in a mendelian randomisation analysis.

PATIENTS AND METHODS

We examined genotypes for rs8044769 in knee or hip OA cases and controls with BMI information coming from seven independent studies (table 1 and see online supplementary methods). These comprised: a subset of knee or hip OA cases from the arcOGEN GWAS versus disease-free controls from TwinsUK, and individuals from the Chingford Study, the Hertfordshire Cohort Study (HCS), the Nottingham Case-Control Study, the Genetics of Osteoarthritis and Lifestyle study, the TwinsUK study and the Tasmanian Older Adult Cohort (TASOAC) study.[2 11 17–22] Cases had either radiographic evidence of the disease with a Kellgren–Lawrence (KL) grade ≥2 or clinical evidence of the disease to a level requiring total joint replacement. Controls were disease-free individuals with KL<2. Individuals from the arcOGEN, Chingford, TwinsUK and the Nottingham cohort with full GWAS information have been subjected to standard GWAS quality control including removal of ethnic outliers. The HCS includes only individuals of self-reported Caucasian origin from within the Hertfordshire county, and TASOAC individuals included in this study are all of self-reported British origin and of white ethnicity (see online supplementary methods). Ethical approval for each study was obtained from the relevant ethical committees and all participants gave written informed consent.

We carried out case/control logistic regression analyses for rs8044769 under the multiplicative model (adjusting for gender and BMI were applicable by including them in the model as covariates) and combined summary statistics in a meta-analysis framework (see online supplementary methods). To evaluate the association of the *FTO* variant with risk of overweight/obese we classified all overweight/obese samples as cases and normal weight subjects as controls in each cohort (irrespective of OA status). For the BMI-matched analyses, we stratified the OA hip or knee cases and the controls into three categories for each cohort according to BMI: normal weight ≤25, overweight and obese >25 and obese only >30.

RESULTS

We analysed genotypes for rs8044769 across a total of 936 normal weight, 2092 overweight and 2381 obese knee OA patients versus 2501 normal weight, 1984 overweight and 877 obese controls and of 1201 normal weight, 1758 overweight and 1396 obese hip OA patients versus 2315 normal weight, 1804 overweight and 848 obese healthy controls from seven independent cohorts from the UK and Australia (table 1). First, we investigated the association of the *FTO* variant with risk of obesity in a case/control analysis of all overweight/obese samples (n=10 538) versus normal weight controls (n=4598) irrespective of OA status and found that to be highly significant. Allele G at rs8044769 was associated with risk of overweight/obesity (BMI≥25) with an OR[CIs]=1.14 [01.08 to 1.19], $p=7.5\times10^{-7}$ and no heterogeneity was observed between studies (heterogeneity index, $I^2=0$). We then examined the strength of association of rs8044769 with knee or hip OA across all OA cases versus controls in each cohort (adjusted for gender) and repeated the analyses adjusting for BMI. A significant association of the *FTO* variant with knee OA only was detected in the meta-analysis without BMI adjustment (OR[CIs]=1.08[1.02 to 1.14], p=0.009) (table 2). The effect of this variant on knee OA is slightly larger and more significant in the analysis of the two genders combined but it appears to be mainly driven by females (see online supplementary table S1) with OR in females=1.07

Table 1 Descriptive characteristics of the study cohorts

		Cases						Controls (OA unaffected)				
Study	Country of origin	OA status	Definition	N	F (%)	BMI±SD [kg/m2]	Age±SD [yrs]	Definition	N	F (%)	BMI±SD [kg/m2]	Age±SD [yrs]
arcOGEN	UK	Hip	KL≥2 or THR	1310	100	28.4±5.8	64.7±9.1	KL<2	1671	100	25.3±4.8	56.8±13.8
arcOGEN	UK	Knee	KL≥2 or TKR	1209	100	30.6±6.3	66.0±8.7	KL<2	1671	100	25.3±4.8	56.8±13.8
Chingford	UK	Hip	KL≥2 or THR	97	100	25.0±3.9	66.0±5.6	KL<2	677	100	24.6±3.5	63.1±5.7
Chingford	UK	Knee	KL≥2 or TKR	266	100	27.1±4.6	65.7±5.9	KL<2	556	100	24.6±3.5	63.1±5.7
GOAL	UK	Hip	KL≥2 or THR	1291	48.7	29.4±5.13	67.8±7.2	KL<2	788	49.7	27.1±4.4	62.7±8.4
GOAL	UK	Knee	KL≥2 or TKR	1619	47.0	30.7±5.4	68.5±7.1	KL<2	788	49.7	27.1±4.4	62.7±8.4
HSC	UK	Knee	KL≥2 or TKR	148	40.1	29.4±5.1	65.2±2.6	KL<2	555	48.9	26.2±3.7	64.8±2.6
Nottingham	UK	Hip	KL≥2 or THR	1525	63.2	27.7±4.7	68.5±9.2	KL<2	750	56.9	26.6±3.9	66.3±9.0
Nottingham	UK	Knee	KL≥2 or TKR	1780	55.3	29.7±5.3	69.0±8,8	KL<2	750	56.9	26.6±3.9	66.3±9.0
TASOAC	Australia	Hip	KL≥2	44	65.1	29.4±5.4	65.4±7.5	KL<2	696	50.4	27.4±4.5	62.3±7.4
TASOAC	Australia	Knee	KL≥2	239	49.8	29.3±5.2	67.3±7.3	KL<2	657	46.0	27.4±4.5	62.3±7.4
TwinsUK	UK	Hip	KL≥2 or THR	88	100	26.0±4.6	57.4±8.0	KL<2	385	100	24.3±4.1	50.3±6.7
TwinsUK	UK	Knee	KL≥2 or TKR	148	100	28.1±5.3	58.8±7.5	KL<2	385	100	24.3±4.1	50.3±6.7

GOAL, Genetics of Osteoarthritis and Lifestyle; TASOAC, Tasmanian Older Adult Cohort.

Table 2 Meta-analysis summary statistics for the association of allele G at rs8044769 with hip or knee OA

OA site	Covariates	N cases/controls	*F.E. OR (95% CIs)	F.E. p value	†R.E. OR (95% CIs)	R.E. p value	‡q p value	§I^2	¶Power
Hip	Sex	4355/4967	1.04 (0.98 to 1.11)	0.170	1.04 (0.97 to 1.12)	0.287	0.328	0.13	0.90
Hip	Sex, BMI	4355/4967	1.00 (0.94 to 1.08)	0.936	0.98 (0.90 to 1.08)	0.749	0.166	0.36	0.90
Hip	Sex, BMI, age	4258/4788	1.00 (0.94 to 1.08)	0.97	1.00 (0.93 to 1.08)	0.929	0.312	0.16	0.89
Knee	Sex	5409/5362	1.08 (1.02 to 1.14)	0.009	1.08 (1.00 to 1.16)	0.056	0.138	0.38	0.94
Knee	Sex, BMI	5409/5362	0.99 (0.93 to 1.05)	0.666	0.99 (0.93 to 1.05)	0.704	0.338	0.12	0.94
Knee	Sex, BMI, age	5228/5183	0.96 (0.90 to 1.03)	0.298	0.97 (0.90 to 1.05)	0.484	0.227	0.26	0.93

*F.E. Fixed effects.
†R.E. Random effects.
‡q_p value Cochran's heterogeneity statistic's p value.
§I^2 Heterogeneity index.
¶Power has been calculated for α=0.05, risk allele frequency=0.5 and effect size=1.1, as estimated in the arcOGEN replication only GWAS.[11]

[1.00–1.15], p=0.049, I^2=0.54 versus OR in males=1.04[0.94–1.14], p=0.47, I^2=0, which is in accordance with the finding reported in the arcOGEN GWAS.[11] After excluding 2323 knee OA cases and 1671 controls that were part of the arcOGEN GWAS discovery study[11] we observe that the effect size is smaller in the replication studies (OR[CIs]=1.04[0.97 to 1.12]) and not significant (p=0.24).

The association signal was fully attenuated after BMI adjustment (table 2) (OR[CIs]=0.99[0.93 to 1.05], p=0.666) in accordance with the finding reported in the full arcOGEN GWAS.[11] Adjusting for age as well as BMI did not make a noticeable difference in these results (table 2). We further investigated the *FTO* association by performing a large-scale meta-analysis across all case/control datasets matched for BMI but observed no evidence for association in any of the BMI strata studied (table 3). The power of our meta-analyses to detect an association between the *FTO* variant rs8044769 and OA is sufficient (>90%) for the knee and hip strata (table 2) but ranges from 0.34 to 0.80 for the hip and knee BMI-stratified analyses (table 3).

We further investigated the direction of causation between overweight status and OA using a mendelian randomisation approach and we computed the summary effect of rs8044769 on overweight status, which results in an OR=1.13[1.07–1.19], ($p=1\times10^{-6}$), and of overweight status on risk of knee OA and hip OA (table 2). Overweight status in the current study samples results in an OR=3.30[3.02–3.62] for knee OA and OR=2.00 [1.82–2.21] for hip OA. We then estimated the expected effect of the G allele on risk of knee OA if the effect on OA is due to the effect of rs8044769 on overweight, which would result in OR=1.16. This value is higher than the upper CI for the observed effect (OR=1.08[1.02–1.14]. The observed effect for hip OA (OR=1.04 [0.98–1.11]) is similar to the expected effect (OR=1.09) of rs8044769.

DISCUSSION

Variation in the *FTO* gene is associated with obesity although the exact mechanism by which *FTO* functions in obesity has not been elucidated. A recent study by the arcOGEN Consortium established an association of rs8044769 at the BMI-associated gene *FTO* and knee and/or hip OA reaching almost genome-wide significance in the female stratum. *FTO* demonstrated expression within OA joint tissues (cartilage, tendon, ligament, meniscus, synovium, fat pad and osteophyte) and control fracture neck-of-femur joint tissues but it is unclear whether its expression is modulated by OA.[11] The discovery and replication studies did not match cases and controls for BMI as the discovery dataset employed population-based controls lacking BMI information. The authors investigated whether the association with this variant was attenuated after adjustment for BMI using a subset of arcOGEN cases and disease-free TwinsUK control data with BMI information and found a substantial attenuation of the association suggesting that the *FTO* gene exerts its effect on OA through obesity. However, due to limited power, no attempt was performed to stratify these analyses by either OA site or BMI category.[11]

Another concomitant report that evaluated the genetic overlap between OA and BMI using fully overlapping samples to the arcOGEN GWAS reported the same conclusion for a variant in the *FTO* locus, rs12149832, which is 3773 kb away and strongly correlated with rs8044769 (r^2=0.7) and is thus likely to represent the same signal.[23] Since it is not clear which causal variant(s) underlie the association between BMI and SNPs in *FTO*[5] and OA and SNPs in *FTO*[11 23] we decided to

Table 3 Meta-analysis summary statistics for the association of allele G at rs8044769 with hip or knee OA across the three BMI strata (normal BMI<25, overweight/obese: BMI≥25, obese: BMI≥30)

OA site	Stratum	N cases/controls	*F.E. OR (95% CIs)	F.E. p value	†R.E. OR (95% CIs)	R.E. p value	‡q p value	§I^2	¶Power
Hip	Normal-weight	1201/2315	1.08 (0.96 to 1.19)	0.190	1.03 (0.88 to 1.21)	0.691	0.105	0.45	0.47
Hip	Overweight/obese	3154/2652	0.97 (0.88 to 1.06)	0.486	0.97 (0.87 to 1.09)	0.602	0.293	0.19	0.73
Hip	Obese	1396/848	1.01 (0.88 to 1.15)	0.939	0.98 (0.73 to 1.31)	0.891	0.007	0.68	0.34
Knee	Normal weight	936/2501	1.00 (0.90 to 1.12)	0.961	0.98 (0.83 to 1.15)	0.804	0.086	0.46	0.42
Knee	Overweight/obese	4473/2861	1.01 (0.93 to 1.08)	0.888	1.01 (0.93 to 1.08)	0.883	0.412	0.02	0.80
Knee	Obese	2381/877	0.97 (0.87 to 1.09)	0.603	0.97 (0.79 to 1.19)	0.777	0.017	0.61	0.40

*F.E. Fixed effects.
†R.E. Random effects.
‡q_p value Cochran's heterogeneity statistic's p value.
§I^2 Heterogeneity index.
¶Power has been calculated for α=0.05, risk allele frequency=0.5 and effect size=1.1, as estimated in the arcOGEN replication only GWAS.[11]

follow-up the association of the variant that showed the strongest evidence for association with OA in the arcOGEN GWAS.[11]

In this study, we have investigated whether rs8044769 is associated with hip or knee OA independently of BMI by performing a large-scale meta-analysis across seven cohorts enabling us to increase the sample size by 55% knee OA cases, 57% hip OA cases and 69% of controls over the discovery study. This gave us sufficient power to perform analyses stratified by joint, joint and gender, and by joint and BMI category, unlike the original report, which examined BMI adjustment in females only. We find no evidence for association between this variant and OA consistent with what is known about the role of the *FTO* gene product, namely, that it is likely to be important to the control of energy homeostasis. As such, it is difficult to envisage a direct influence on the development of a joint pathology like OA except through its role on body mass.

The data presented here can be interpreted in the context of mendelian randomisation supporting the causal role of overweight on OA. Although the association between BMI and OA is well known, it could be a comorbidity that accompanies the disease.[14 15] The genetic results shown by our study indicate that, on the one hand, overweight appears to be indeed causative of OA as we find an association between OA and *FTO*, which is fully accounted for by the role of *FTO* on overweight and disappears once we adjust for BMI or for BMI stratum. Furthermore, the observed and expected associations between *FTO* and hip OA are very similar. On the other hand, we observe a larger correlation between overweight on knee OA than what can be explained merely if overweight is causative of knee OA suggesting that there may be synergistic effects between overweight and knee OA due to, for example, lifestyle factors or lack of mobility. Hence, although overweight may be a cause of OA, the comorbidity and lack of mobility that results from knee OA may be resulting in further risk of overweight.

We note some study limitations. First, the statistical power of the current study to detect association of the *FTO* SNP and OA is sufficient in the overweight stratum (73%–80%) but is modest for the normal weight and obese strata (34%–47%). Thus, we cannot exclude the possibility that a very modest association may be present among normal weight individuals, which our study failed to detect. On the other hand, overweight individuals constitute the majority of OA cases and represent over 70% of the total joint replacement cases.[2] The fact that our study finds no evidence of association with *FTO* in the overweight stratum despite being sufficiently-powered, suggests no direct implication of the *FTO* gene in susceptibility to OA. We also note that our study has combined both OA cases from population-based cohorts and severe OA cases from case/control studies recruited via secondary care (see online supplementary methods). However, we believe that this does not present a limitation of the current study because in the arcOGEN GWAS the *FTO* variant was more strongly associated when all cases (ascertained either by radiography or by total joint replacement) were included in the analysis.[11]

In summary, unlike the original report of the *FTO* association with OA, which was able to adjust for BMI only on a modest subset of female cases and controls, the present study gives a definitive answer showing that the effect of this variant on OA is solely due to its effect on BMI. Moreover, having tested the association in the context of mendelian randomisation, the results in this report indicate that overweight is on the causal pathway to OA rather than the inverse, although OA-induced inactivity may also be having an adverse effect on knee OA.

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Contributors All authors contributed to the study design, data interpretation and the final manuscript. In addition GJ, LLL, SAD, MD, TS, NKA and MW evaluated study subjects. AMV and KP analysed and interpreted the data and prepared the manuscript. AMV supervised the study.

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