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The *FTO* gene polymorphism is associated with end-stage renal disease: two large independent case–control studies in a general population

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Abstract

Background. Genome-wide association studies identified the *FTO* (fat mass and obesity gene) gene as an important determinant of body weight. More recently, the *FTO* gene was reported to be associated with other outcomes, including major risk factors for chronic kidney disease (CKD). We investigated the role of this gene in the risk of end-stage renal disease (ESRD) caused by CKD.

Methods. We conducted two large population-based case–control studies of ESRD. Study 1 compared 984 haemodialysed patients with ESRD with 2501 participants in the Czech post-MONICA study; Study 2 compared 1188 patients included in a kidney transplantation programme for ESRD with 6681 participants in the Czech HAPIEE study. The frequencies of the *FTO* rs17817449 single nucleotide polymorphism genotype were compared between cases and controls.

Results. The *FTO* rs17817449 genotype was significantly associated with CKD in both studies (P-values 0.00004 and 0.006, respectively). In the pooled data, the odds ratios of CKD for GG and GT, versus TT genotype, were 1.37 (95% confidence interval 1.20–1.56) and 1.17 (1.05–1.31), respectively (P for trend <0.0001). Among haemodialysed and kidney transplant patients, the onset of ESRD in GG homozygotes was 3.3 ($P = 0.012$) and 2.5 ($P = 0.032$) years, respectively, earlier than in TT homozygotes.

Conclusions. These two large independent case–control studies in the general population found robust associations between the *FTO* rs17817449 polymorphism and the ESRD. The results suggest that the morbidities associated with the *FTO* gene include CKD.

Keywords: chronic kidney disease; end-stage renal disease; FTO; genetic epidemiology

Introduction

Genome-wide association studies identified variations in the first intron of the *FTO* (fat mass and obesity associated) gene as genetic risk factors for obesity in a wide range of populations [1–4]. The *FTO* gene (ID 79068, OMIM acc. N. 610966) codes a protein, the exact role of which remains unknown, but the *FTO* gene is widely expressed in human tissues, and some experiments suggest that *FTO* gene products exhibit slight and different enzymatic activities, namely 2-oxoglutarate-

dependent nucleic acid demethylase activity [5] and non-haeme dioxygenase activity [6]. The research on *FTO* has primarily concentrated on its association with obesity and body mass index (BMI) values, food intake and energy expenditure [7].

More recently, a large cohort of Danish men reported an association between the *FTO* single nucleotide polymorphism and all-cause mortality [8]. The effect of the *FTO* gene appeared similar in obese and lean individuals, its magnitude was comparable with that of smoking, and the gene was not associated with a particular cause of death. Other recent reports suggest that the *FTO* variants are associated with a range of conditions, such as cancer [9], diabetes [10], hypertension [11], polycystic ovaria [12], acute coronary syndrome [13], metabolic syndrome [14], Alzheimer disease [15] and reduced brain volume [16]. Taken together, these recent reports imply a pleiotropic effect of the *FTO* gene (i.e. that its effects are not limited to body weight or obesity).

Chronic kidney disease (CKD) has become a major public health problem due to its high prevalence, enormous cost and reduction in patients' life expectancy and quality of life [17]. The majority of CKD, leading to end-stage renal disease (ESRD), is closely linked to diabetes and hypertension; virtually, all patients with ESRD have diabetes, hypertension or both [17, 18]. Other risk factors for ESRD include history of cardiovascular disease (CVD), which has led to a proposition that CKD primarily reflects vascular disease [19]. Besides environmental/external factors, inherited/genetic dispositions have been suggested to influence the progression of CKD and ESRD development. Previous studies detected a strong genetic component of ESRD, with heritability ranging from 0.30 to 0.44 [20]. Indeed, several genetic polymorphisms affecting CKD/ESRD development have already been detected [21], but the current knowledge about the genetic determinants of CKD/ESRD is far from complete.

Given the fact that majority of ESRD is caused by diabetes and hypertension, which in turn is related to conditions linked with the *FTO* gene, an association between ESRD and *FTO* is plausible. To expand our understanding of the morbidities associated with the *FTO* gene, we have investigated whether there is a relationship between CKD/ESRD and the *FTO* polymorphism and whether the *FTO* genotype was associated with the age of onset of ESRD in patients with CKD.

Materials and methods

We conducted two independent case–control studies in the Czech Republic, using two different groups of patients with CKD/ESRD and two different sets of population-based controls. The local Ethical Committees of the Institute for Clinical and Experimental Medicine in Prague, Czech National Institute of Public Health and University College London approved the protocol of these studies. All subjects included in the study were Caucasian, and all gave their informed consent to participate in the study.

Study 1

In the first study, there were 1014 cases (56% males, mean age 66.9 ± 12.7 years) from 27 haemodialysis centres in the Czech Republic. The prevalence of drug-treated hypertension was 63%, prevalence of diabetes was 39% and the mean BMI at the time of the inclusion into the study was 26.2 (±5.0) kg/m^2 (BMI was available for 64.2% of patients). To be included in the study, the patients had to be on dialysis therapy for at least 3 months, and they had to give consent to participate in the study. Patients with generalized cancer, history of poisoning or another known exogenous cause of ESRD were excluded from the study.

The controls in Study 1 were 2559 individuals without CKD/ESRD (49% males, mean age 49.0 ± 10.7 years) who participated in the post-MONICA study [22]. The post-MONICA study, using the WHO MONICA Project protocol [23], examined a 1% random population sample of men and women aged 25–64 years in nine Czech districts in 1997/1998; the subjects were re-examined in 2000/2001, when blood samples used for DNA extraction were taken.

Study 2

In the second study, there were 1251 cases (65% males, mean age 47.2 ± 13.0 years) who underwent kidney transplantation for CKD/ESRD at the Institute of Clinical and Experimental Medicine in Prague in 1999–2007. Among those cases, prevalence of drug-treated hypertension was 82%, prevalence of diabetes 35% and mean BMI at inclusion to study 25.5 kg/m^2 (BMI was available for 50.6% of the patients). Patients were referred for kidney transplantation by the same dialysis centres that provided cases for the first study. The blood samples for DNA extraction were drawn during hospitalization for kidney transplantation.

The control group consisted of participants from the baseline survey of the Czech HAPIEE study conducted 2002–05 [24]. The participants, men and women aged 45–69 years, were randomly selected from population registers of seven Czech towns. DNA samples are available for 6827 (45% males, mean age 58.2 ± 7.1 years) individuals.

Genotyping

The *FTO* gene variant rs17817449 (which is in almost complete linkage disequilibrium with other often analysed variants rs9939609 and rs1421085) was analysed by polymerase chain reaction (PCR) and restriction analysis [25, 26]. Briefly, genotyping of the rs17817449 variant was performed by PCR using oligonucleotides 5′ ggt gaa gag gag gag att gtg taa ctg g 3′ and 5′ gaa gcc ctg aga agt tta gag taa att ggg 3′ followed by treatment with restriction enzyme AlwNI (uncut PCR product 198 bp represents allele G, restriction fragments of 99 and 99 bp allele T). The genotype call rates were 97.0% in haemodialysed cases and 96.4% in post-MONICA-based controls in Study 1 and 96.9% in kidney transplantation cases and 97.9% in the HAPIEE study-based controls in Study 2. To ensure the accuracy of the method, one plate (94 samples) was genotyped twice within 1 week; the agreement between the two analyses was 100%. The reliability of the genotyping results is further supported by the fact that the allele frequencies were very similar to those previously reported in western European populations [1–3, 8].

Statistical analyses

The statistical analyses are based on subjects with valid *FTO* genotype data (and reflecting the call rates described above); there were 984 cases and 2501 controls in Study 1 and 1188 cases and 6681 controls in Study 2.

The Hardy–Weinberg test was applied to confirm independent segregation of the *FTO* alleles. There was a borderline significant deviation of the *FTO* genotype frequencies from the Hardy–Weinberg equilibrium (HWE) for the controls in Study 2 from the HAPIEE study ($P = 0.03$).

The differences in the genotype frequencies between cases and controls were assessed by chi-square and likelihood ratio tests. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were estimated using the STATA software. In the primary analyses, the association between the *FTO* genotype and ESRD was assessed in each case–control study separately; after that, we also analysed the pooled data (i.e. both groups of cases combined versus both control groups combined). The relationship between the age of onset of CKD and the *FTO* genotype was analysed using analysis of variance and linear regression. The pooled dataset provided a statistical power of >95% to detect an OR of ≥1.25, for GG versus TT genotype at 95% confidence level.

Results

In both sets of healthy controls, the *FTO* genotype was associated with BMI in the expected direction; i.e. the carriers of the GG genotype had significantly higher BMI than carriers of GT and TT alleles [25, 26]. Among cases, data

Table 1. Frequencies of the *FTO* rs17817449 genotypes in cases and controls and ORs (95% CIs) for ESRD by *FTO* genotype

	Study 1			Study 2			Pooled data		
	Cases, *N* (%)	Controls, *N* (%)	OR (95% CI)	Cases, *N* (%)	Controls, *N* (%)	OR (95% CI)	Cases, *N* (%)	Controls, *N* (%)	OR (95% CI)
TT	273 (28%)	829 (33%)	1.0	350 (29%)	2204 (33%)	1.0	623 (29%)	3033 (33%)	1.0
GT	487 (49%)	1240 (50%)	1.19 (1.00–1.42)	578 (49%)	3188 (48%)	1.14 (0.99–1.32)	1065 (49%)	4428 (48%)	1.17 (1.05–1.31)
GG	224 (23%)	432 (17%)	1.56 (1.27–1.96)	260 (22%)	1289 (19%)	1.27 (1.07–1.51)	484 (22%)	1721 (19%)	1.37 (1.20–1.56)
P (chi-square)			0.0002			0.024			<0.0001
P for trend			<0.0001			0.006			<0.0001

on BMI before the onset of CKD were not available. However, BMI was available for a subset of cases at the time of the inclusion into the haemodialysis/transplantation programme. Similar to the controls, the *FTO* G allele was positively associated with BMI both in haemodialysed and transplant patients.

The main results are shown in Table 1. There are several notable findings. Firstly, the frequencies of the *FTO* genotypes differ significantly between cases and controls in both studies, and in both studies, the OR of ESRD/CKD increases with the number of G alleles. In Study 1, the OR of ESRD/CKD for GG homozygotes compared with TT homozygotes was 1.56 (95% CI 1.27–1.96), and trends of increasing OR with increasing number of G alleles were highly significant (P = 0.00004). In Study 2, the results were similar, although the association was weaker than in Study 1; the OR of ESRD for GG versus TT genotype was 1.27 (95% CI 1.07–1.51), and the P-value for trends was 0.006.

Secondly, there were no significant differences in the frequencies of the *FTO* genotypes between the two sets of cases (P = 0.60) and between the two sets of controls (P = 0.07).

Finally, cross analyses produced results consistent with those found in the primary analysis; the ORs of ESRD for GG versus TT genotype were 1.42 (95% CI 1.16–1.72, P for trend 0.00099) for comparing cases from Study 1 with controls in Study 2 and 1.40 (95% CI 1.15–1.70, P for trend 0.00036) for comparing cases from Study 2 with controls in Study 1. Given these results, it is not surprising that there was a highly significant association between the *FTO* genotype and ESRD/CKD in data pooled from both studies (2196 cases and 9048 controls). The OR for GG versus TT genotype was 1.37 (1.20–1.56), and the trend for increasing OR with increasing number of G alleles was highly significant (P = 0.000011). Further adjustment for age and sex did not materially change these estimates; the ORs for GG and GT versus TT genotypes were 1.34 (1.16–1.54) and 1.13 (1.00–1.47), respectively.

In addition to the case–control comparisons, we have also examined whether the age of onset of ESRD differs by *FTO* genotype in a subset of 753 haemodialysed and 1095 kidney transplantation patients of whom the age of onset was available (Table 2). We found that in haemodialysed patients (cases from Study 1), the age at onset of ESRD was significantly associated with *FTO* genotype; the onset of the disease in carriers of the G allele was ~3 years earlier than in TT homozygotes. The association in kidney transplant patients (cases from Study 2) was similar: GG homozygotes had onset of ESRD ~2.5 years earlier than TT homozygotes. Additional adjustment for presence of diabetes and sex did not change these results significantly (not shown in table).

Table 2. Mean age (SD) at onset of ESRD in cases from Study 1 and Study 2 by *FTO* genotype[a]

	Haemodialysed patients (cases from Study 1), *N* = 753	Kidney transplantation patients (cases from Study 2), *N* = 1095
TT	63.5 (13.3)	47.9 (13.3)
GT	59.9 (13.9)	47.3 (12.8)
GG	60.1 (14.6)	45.4 (13.2)
P-value (ANOVA)	0.008	0.071
P-value (trend)	0.012	0.032

[a]ANOVA, analysis of variance.

Discussion

It is known that both genetic and environmental factors contribute to CKD/ESRD risk and both are of significant importance [20, 21]. As in other diseases, the vast majority of CKD/ESRD risk is under polygenic control, with many variants in a number of genes contributing to the total effect, each with a small, but detectable effect, in studies with sufficient power. The genes previously studied in association with CKD/ESRD and its complications include apolipoprotein E, methylentetrahydropholate reductase, interleukins and tumour necrosis factor alpha [27]. This is the first report that examines the possible role of the *FTO* gene. Our results, based on two large independent sets of cases and controls selected from general central European Slavonic population, comprising in total >2000 cases and almost 10 000 controls, suggest a robust association between the *FTO* genotype and the risk of CKD/ESRD. We also found a suggestion of an earlier onset of ESRD in carriers of the G allele.

To our knowledge, this is the first study explicitly investigating this topic, although there are some indirect indications from other studies (see below). This study has several important strengths. Firstly, the large sample size means that the study had a large enough statistical power to detect modest effects. Secondly, we analysed two different sets of cases and controls and effectively replicated the main

finding in an independent investigation. This greatly reduces the possibility that the results are due to chance (false positive).

Thirdly, this study was population based. Although the cases came from medical centres, the nature of ESRD (requiring referral for haemodialysis or transplantation) means that the cases were population based rather than drawn from specific sub-populations. Controls were random population samples. While, strictly speaking, controls and cases were not recruited from identical geographical areas, the fact that the controls were not selected on the basis of their health status reduces the scope for selection bias.

There are several limitations of this study. Firstly, we did not have more details about the cases. To recruit large numbers of cases, we had to compromise on the amount of data about them e.g. details about their health behaviours, other risk factors and clinical and laboratory data. Some of this information was available for subsets of both sets of cases, but because it was not collected in a comparable fashion with controls, these data do not allow detailed statistical analyses. Moreover, even if such data were available, they would reflect the patients' status at a very late stage of CKD; this would be insufficient to estimate the role of, for example, diabetes and hypertension, in the development of the disease.

Secondly, ~50% of the cases did not undergo renal biopsy in the phase of ESRD; therefore, exclusion of potential exogenous causes of the CKD may not be reliable. However, it has been estimated that at least 75% of CKD cases are due to diabetes and hypertension [17], while other causes, such as cancer or poisoning, are relatively uncommon (and patients suffering from cancer or poisoning were not included in our study). While we could not reliably exclude all such secondary CKD from our study, their presence would probably lead to underestimation of the association between *FTO* and ESRD (assuming that the secondary CKD is not associated with the *FTO* gene). Our estimates of the effect of the *FTO* genotype are therefore likely to be realistic.

Finally, the distribution of the genotypes among controls in Study 2 was not in HWE. This can be partly explained by chance and high statistical power (even modest differences between expected and observed frequencies are statistically significant with sufficiently large numbers of subjects, and the P-value in our study was of a borderline significance). The literature suggests that the most common reason of Hardy-Weinberg disequilibrium in genetic association studies is genotyping error [28]. Our quality control did not suggest any problem with genotyping, and the relationship between *FTO* and BMI was similar in both sets of controls. The main difference between the observed and HWE expected genotype frequencies among the controls in Study 2 was the proportion of GT heterozygotes (47.7% in observed data versus 49.1% in expected data), while the observed and expected proportions of GG and TT homozygotes were similar to the expected. Moreover, the OR of ESRD based on the expected frequencies among controls in Study 2 was 1.29, which is slightly higher than the observed OR of 1.27. These sensitivity calculations suggest that the association between *FTO* and ESRD was not overestimated in Study 2.

The finding that, among haemodialysis patients, the GG homozygotes had lower age of CKD/ESRD onset than the TT homozygotes is consistent with the results of our two case–control studies. This was replicated in transplant patients, although in this group the difference in age of onset was somewhat smaller. This may be due to the fact that transplant patients are generally younger and have lower rates of diabetes, CVD and other comorbidities than patients with ESRD not selected for transplantation. This was also the case in our study; transplant patients represent a healthier pre-selected group of CKD/ESRD patients, and this may explain the weaker association between the *FTO* polymorphism and the age of onset of ESRD.

It is difficult to assess the consistency of our findings with previous studies, because the existing literature on *FTO* and CKD/ESRD is sparse. We identified only two sets of reports in the literature, and they are only partly relevant. Firstly, using two Korean studies analysing the *FTO* variant rs8050136, 629 healthy controls from a study by Cho *et al.* [29] were compared with 583 kidney transplantation patients from a separate independent study [30]. In this comparison, kidney transplant patients had a frequency of the less common allele of 25%, which is slightly higher than the 22.7% among healthy non-diabetic subjects; however, the OR 1.14 is not statistically significant, mainly because of the relatively small numbers of individuals in both groups. However, these Korean data are based on a population with a different ethnic background and using different *FTO* gene polymorphisms with different allelic frequencies and cannot be directly compared with our study. The second study investigated the role of the *FTO* gene variant (rs9939609) in the development of diabetic nephropathy in diabetic patients [31]. While the *FTO* genotype was associated with BMI, it was not related to the risk of nephropathy. This study, however, did not focus on the relation between ESRD and the *FTO* gene.

While the association between the *FTO* genotype and ESRD in our data is statistically robust, we can only speculate about the biological basis for this link. It is known that *FTO* is associated with obesity and diabetes mellitus and both these conditions are risk factors of CKD/ESRD development. It is possible that the *FTO* effect on CKD/ESRD is at least partly mediated through these conditions. However, pathways independent from diabetes and obesity are also likely, in analogy to earlier studies that showed that the *FTO* genotype was related to the risk of acute coronary syndrome after controlling for BMI and diabetes [13] or with increased mortality independently of BMI [8].

The gene translation product of *FTO* exhibits more enzymatic activities, but the real function of FTO remains largely unknown and is a matter of speculation. As *FTO* was originally identified as a determinant of obesity, functional studies have focused on the possible associations of the *FTO* gene variants with the preference of energy-dense food, with higher fat intake or with markers of physical activity. While the association of *FTO* with higher energy intake has been replicated in children and adolescents, it seems unlikely that the *FTO* gene affects the development of CVD or ESRD through this mechanism.

Alternatively, the *FTO* polymorphisms may enhance the risk of ESRD through its possible effect on DNA methylation (i.e. the epigenetic status). There is strong experimental evidence that the *FTO* gene could be involved in demethylation of the 1-methyladenine and 3-methylcitosine [32]. In addition, animal experiments suggest that nutrition and other life style factors significantly affect the methylation (epigenetic) status of many genes, which play a significant regulatory role in wide spectrum of human diseases [33, 34] and which may include genes influencing ESRD. Since the *FTO* gene codes protein with slight 2-oxoglutarate-dependent nucleic acid demethylase activity [5], it could provide the link between life style and risk of chronic diseases. Finally, at least in some conditions (newborns with low weight for gestational age; other individuals were so far not studied), it was proven that *FTO* variants within the first intron are associated with different methylation status of the peroxisome proliferator-activated receptor gamma gene promoter [35].

Despite the uncertainty about biological mechanisms, there is strong evidence that the *FTO* genotype is associated with obesity and there is emerging evidence that the *FTO* gene is related to several other health outcomes. This well-powered population-based case–control study suggests that the *FTO* polymorphism is also associated with CKD. Further studies are required to replicate this association in other populations and to clarify the molecular and pathophysiological mechanisms.

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Conflict of interest statement. None declared.

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