Received: 3 February 2019 | Revised: 29 August 2019 | Accepted: 3 September 2019

DOI: 10.1002/mgg3.985

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Genetics of diabetic kidney disease: A follow-up study in the Arab population of the United Arab Emirates

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Funding information
Khalifa University Internal Research Fund

Abstract

Background: Two genome-wide association studies in European and Japanese populations reported on new loci for diabetic kidney disease (DKD), including *FTO*. In this study, we have replicated these investigations on a cohort of 410 Type 2 diabetes mellitus (T2DM) patients of Arab origin from the United Arab Emirates (UAE).

Methods and Results: The cohort included 145 diabetic patients diagnosed with DKD and 265 diabetics free of the disease. In general, we were able to confirm the association between the *FTO* locus and DKD, as reported in the Japanese population. Specifically, there were significant associations with two single nucleotide polymorphisms (SNPs), namely rs1421086 ($p = .013$, OR = 1.52 depending on allele G, 95% CI: 1.09–2.11) and rs17817449 ($p = .0088$, OR = 1.55 depending on allele C, 95% CI: 1.12–2.14) of the *FTO* locus. Both SNPs were in linkage disequilibrium with rs56094641, also as reported in the Japanese population. While the alleles of both SNPs, which increase the risk of DKD, were associated with higher Body Mass Index (BMI), their associations with DKD were independent of the BMI effects.

Conclusions: This study confirms that *FTO* is a multiethnic locus for DKD which is independent from any influence of BMI and/or obesity.

KEYWORDS
diabetic kidney disease, *FTO*, genetics, Type 2 diabetes, United Arab Emirates

1 | INTRODUCTION

Diabetic kidney disease (DKD) is a common complication of both Type 1 and Type 2 diabetes mellitus (T2DM). In patients with T2DM, the risk of DKD is approximately 2% per year of the disease (Gross et al., 2005). The prevalence of DKD in patients with T2DM is variable depending on several factors, including ethnicity (Thomas et al., 2015). The prevalence of DKD in Arab populations is also variable and ranges from 10.8% to 61.2% (Aldukhayel, 2017); being reported as ~6% in the United Arab Emirates (UAE) among patients with T2DM (Jelinek et al., 2017).

We have recently reported that the duration of the T2DM was the most significant risk factor related to the development of DKD in the Arab population of the UAE (Osman, Jelinek, et al., 2018). We have also confirmed that among the 43 genetic loci linked to DKD and included in the study, the *SHROOM3* locus was the only locus with associations with DKD patients from UAE (Osman, Jelinek, et al., 2018).

Recently, two genome-wide association studies in a Japanese population (Taira et al., 2018) and a European population (van Zuydam et al., 2018) reported associations with new genetic loci for DKD. Among these, significant associations were reported with *GABRR1, UMOD,* and *PRKAG2* in Europeans (van Zuydam et al., 2018) and with *FTO* in the Japanese cohort (Taira et al., 2018), in addition to additional six highly suggestive associations in the Japanese population. These loci have not been considered in individuals of Arabian ancestry. Therefore, our aim was to investigate the associations of these newly reported loci in the UAE Arab population.

2 | METHODS

2.1 | Ethical compliance

Each patient agreed to take part in this study and provided an informed signed consent after a brief session to explain the aims and methods. The study was approved by the Institutional Ethics Committees of Mafraq and Sheikh Khalifa Medical Centre hospitals (REC-04062014 and R292, respectively) and conformed to the ethical principles outlined in the Helsinki declaration.

2.2 | Patients and demographic data

This report describes a cross-sectional study of Emirati patients from the city of Abu Dhabi. The details regarding the T2DM patients, their demographic information, clinical data, and DKD characterization are all summarized in our previous report (Osman, Jelinek, et al., 2018). Participants were recruited from Mafraq and Sheikh Khalifa Medical City Hospitals, Abu Dhabi, UAE. In total, 145 T2DM patients with DKD and 265 without DKD met the criteria for inclusion in this study. The demographic data are shown in Table 1.

2.3 | Patient and public involvement

The study was designed as a follow-up for our previous study in DKD in the UAE, which constitutes a major health problem. However, patients and the public at large were not involved in defining the research questions, analyses, interpretation, or dissemination of the results.

2.4 | Selection of SNPs

Single nucleotide polymorphisms (SNPs) summarized in Table 2 were selected based on the results of the previous two genome-wide studies for DKD (Taira et al., 2018; van Zuydam et al., 2018). For the SNPs which were not available for analysis in our T2DM cohort (Alsafar, Jama-Alol, Hassoun, & Tay, 2012), we selected proxy SNPs depending on their Linkage Disequilibrium ($r^2 > .8$) with the original index SNPs using data from the European samples collected in phase 3 of the 1,000 genome project and stored in the rAggr database (http://raggr.usc.edu/), as a reference. For the *FTO* rs56094641, we included two proxies; rs1421085 which is the strongest linked SNP in our database, and rs17817449 because it was reported to be associated with end-stage renal disease (ESRD) by Hubacek et al. (2011).

2.5 | Statistical analyses

PLINK software version 1.07 (http://zzz.bwh.harvard.edu/plink/) was used for counting allele frequencies and testing the quality control (QC) variables, including Hardy–Weinberg equilibrium. The same software was also used for testing the associations between the SNPs and DKD using a logistic regression model with assumption of additive effect. The model included age, gender, log Body Mass Index (BMI), and T2DM duration as covariates, as previously reported, to avoid bias (Taira et al., 2018; van Zuydam et al., 2018). The results are presented as *p*-values and odds ratios with corresponding 95% confidence intervals. As this was a

TABLE 1 Demographic data of 410 participants

Variable	DKD	No DKD	p^a
Gender: Female	70 (48.3%)	165 (62.3%)	.006
Age (years)	67.0 ± 10.4	58.6 ± 10.6	<.0001
Diabetes duration (years)	16.0 ± 9.2	10.1 ± 7.3	<.0001
BMI (kg/m^2)	31.3 ± 6.0	32.5 ± 6.3	.078

Abbreviation: DKD, diabetic kidney disease.

[a]*p*-value for continuous data, calculated using two-sided *t*-test and for percentage data calculated using Pearson chi-squared test.

TABLE 2 SNPs tested in this study and selection of proxy SNPs for missing index SNPs

Original SNP	Chr	Gene	OMIN accession no	Tested SNP	r^2	D'	Distance[a]
rs9942471	6	*GABRR1*	* 137,161	rs1186903	0.95	1	20.661
rs11864909	16	*UMOD*	* 191,845	Index			
rs10224002	7	*PRKAG2*	* 602,743	rs7805747	0.88	0.96	7.240
rs56094641	16	*FTO*	* 610,966	rs1421085	0.98	1	5.499
rs56094641	16	*FTO*	* 610,966	rs17817449	0.92	1	−6.914
rs895157	17	*PRCD*	* 610,598	rs752049	0.81	1	−6.022
rs10144968	14	*RAD51B*	* 602,948	rs6573851	0.99	1	1.023
rs7544082	1	*TRABD2B*	* 614,913	Index	—	—	—
rs11101179	10	*CHAT*	* 118,490	Index	—	—	—
rs710375	5	*CCNH-TMEM161B*	* 601953- #613443	Index	—	—	—
rs13306536	1	*LRP8*	* 602,600	Not a SNP in UAE population	—	—	—

Abbreviation: Chr, chromosome.
[a]Distance between proxy and original SNPs in kilo base pair.

replication study, $p < .05$ were considered as a replication. However, considering the Bonferroni correction for multiple testing, the p-values are statistically significant at $p < .005$ (0.05/10).

2.6 | Statistical power considerations

Power calculations were done based on the current sample size (145 patients with T2DM and DKD vs. 265 patients with T2DM but without DKD), prevalence of DKD in the UAE population ~6% (Jelinek et al., 2017), genotype risk for each SNP, as reported previously (Taira et al., 2018; van Zuydam et al., 2018), significance level of 0.05 (assuming testing individual markers separately), disease allele frequency for each tested SNP, as reported in this study, and multiplicative model. Full details of power calculations are shown in Table S1. Accordingly, power of different SNPs, in this study, ranged from ~13% to 37%. These power calculations were performed using the Genetic Association Study Power Calculator (http://csg.sph.umich.edu//abecasis/cats/gas_power_calculator/index.html).

3 | RESULTS

Nine genetic loci were included in the analysis. These include three loci which were previously reported in the European population (van Zuydam et al., 2018), in addition to six reported in the Japanese population (Taira et al., 2018). The SNP rs13306536 in *LRP8* is not polymorphic in the UAE population (Table 2). Following adjustment of covariates (**see Methods Section**), two SNPs in *FTO* showed significant associations with DKD; namely, rs1421086 ($p = .013$, OR = 1.52 depending on allele G, 95% CI: 1.09–2.11) and rs17817449 ($p = .0088$, OR = 1.54 depending on allele C, 95% CI: 1.12–2.14), Table 3. The SNP rs1421086 was included in this analysis as the best proxy for rs56094641 in our database ($r^2 = .98$, $D' = 1$), and rs17817449 was included because it is both highly linked to rs56094641 and reported to be associated with end-stage renal disease (ESRD) (Hubacek et al., 2011). The association results of both SNPs remained significant without adjustment for BMI; rs1421085 ($p = .014$, OR = 1.51 depending on allele C, 95% CI: 1.09–2.1) and rs17817449 ($p = .013$, OR = 1.51 depending on allele C, 95% CI: 1.09–2.08).

4 | DISCUSSION

Diabetes Kidney Disease is a leading cause of ESRD. In the Arabian peninsula, DKD is responsible for approximately 17% of ESRD cases (Hassanien, Al-Shaikh, Vamos, Yadegarfar, & Majeed, 2012). Genetic factors are expected to influence the development of DKD, as the disease tends to have a familial clustering (Fava, Azzopardi, Hattersley, & Watkins, 2000; Krolewski, 1999). Since the UAE has one of the highest incidences of T2DM (Alsafar et al., 2012) and diabetes complications (Jelinek et al., 2017) in the world, it is important to understand the pathophysiological factors underlining these conditions, including genetic factors.

Few studies with solid associations have been reported in the Literature. However, in 2018, two genome-wide studies with a significant number of patients were published (Taira et al., 2018; van Zuydam et al., 2018). This study aimed to replicate these works, although in the current report, only one locus, *FTO*, was investigated. Some risk alleles for DKD, such as rs1421085 ($p = .07$, coefficient = 0.01) and rs17817449 ($p = .0034$, coefficient = 0.016), also tend to have higher BMI following adjustment for age and gender. However, the associations of both rs1421085 and rs17817449 with DKD

TABLE 3 Results of replication analyses of recent genome-wide studies of diabetic kidney disease in the UAE cohort

SNP	Chr: BP	Gene	A1/A2	Case		Control		P_{HWE}[a]	OR[b] (95% CI)	p[c]
				Exact Genotypes	*MAF*	*Exact Genotypes*	*MAF*			
rs1186903	6:89927571	*GABRR1*	A/G	11/63/71	0.293	31/101/133	0.308	0.09	1.00 (0.71–1.42)	.98
rs11864909	16:20400839	*UMOD*	A/G	11/47/87	0.238	17/79/169	0.213	0.07	1.17 (0.81–1.69)	.4
rs7805747	7:151407801	*PRKAG2*	A/G	6/42/97	0.186	16/71/177	0.195	0.03	0.96 (0.65–1.42)	.82
rs1421085	**16:53800954**	***FTO***	**G/A**	**31/77/37**	**0.479**	**53/117/95**	**0.421**	**0.14**	**1.52 (1.09–2.11)**	**.013**
rs17817449	**16:53813367**	***FTO***	**C/A**	**34/73/38**	**0.486**	**52/116/97**	**0.415**	**0.13**	**1.55 (1.12–2.14)**	**.0088**
rs752049	17:74546939	*PRCD*	T/C	18/51/76	0.3	24/109/132	0.296	0.88	1.1 (0.78–1.54)	.6
rs6573851	14:69149862	*RAD51B*	G/A	8/42/95	0.2	15/90/160	0.226	0.6	0.89 (0.61–1.32)	.57
rs7544082	1:48203990	*TRABD2B*	A/C	8/58/79	0.255	21/99/145	0.266	0.53	0.96 (0.66–1.4)	.84
rs11101179	10:50810891	*CHAT*	G/A	19/49/77	0.3	22/77/166	0.228	0.005	1.11 (0.79–1.55)	.56
rs710375	5:87082276	*CCNH-TMEM161B*	A/G	43/56/46	0.49	64/127/74	0.48	0.53	1.12 (0.66–1.4)	.84

Abbreviations: A1/A2, alleles 1 & 2; BP, base pair; CI, confidence intervals; Chr, chromosome; MAF, minor allele frequency; OR, odds ratio.

[a]P-value of Hardy–Weinberg Equilibrium (HWE) in the control group.

[b]Odds ratio is based on allele 1 (A1), which is the minor allele. Corresponding exact genotype counts also follow minor: major alleles.

[c]*p*-value of the logistic regression analyses adjusted for age, gender, log BMI, and diabetes duration. Significant results are shown in bold.

were independent of the BMI values in the current study. This is in line with the results of Taira et al. (2018). These results suggest that *FTO* seems to influence DKD through a mechanism other than obesity, which is a known risk factor for chronic kidney disease (Wickman & Kramer, 2013). In fact, both SNPs also remained associated with DKD even following adjustment for hypertension and estimated Glomerular Filtration Rate (data not shown).

The risk allele frequency of both SNPs, and hence rs56094641, is high in the UAE Arab population in comparison with the Japanese population, ranging from 0.4 to 0.42, which is similar to some European populations (**see NCBI database**). In this sense, obesity rates in the UAE are also high (Katsaiti & El Anshasy, 2013), and *FTO* is consistently associated with obesity in the UAE population (Khan, Chehadeh, Abdulrahman, Osman, & Al Safar, 2018; Osman, Tay, & Alsafar, 2018).

Finally, in spite of the fact that this study had a relatively small sample size and a study power ~30% of *FTO* SNPs, the association of *FTO* with DKD was validated using two separate SNPs in individuals of Arab origin. A limitation for to this study was that the analyses carried out did not include treatment modalities due to patients having multiple conditions and treatments, which made the models unstable and difficult to interpret.

AUTHOR CONTRIBUTION

HSA obtained the funding for this study. WMO, HSA, and HFJ designed the study. WMO analyzed the data and prepared the manuscript. HFJ, GKT, AHK, and KK provided critical revision the manuscript, contributed to writing the discussion, and writing the revision of the manuscript. WA and MHH did the patient recruitment process and provided acquisition clinical data collection. All authors gave final approval of the version to be published.

CONFLICT OF INTERESTS

None declared.

FUNDING INFORMATION

This study was supported by research incentive funds from Khalifa University Internal Research Fund Level 2 granted to Dr. Habiba Al Safar. No role of funders taken in this study.

DATA AVAILABILITY STATEMENT

No additional data are available.

ETHICS APPROVAL

The Institutional Ethics Committee of Mafraq and Sheikh Khalifa Medical Centre hospitals (REC-04062014 and R292, respectively).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Osman WM, Jelinek HF, Tay GK, et al. Genetics of diabetic kidney disease: A follow-up study in the Arab population of the United Arab Emirates. *Mol Genet Genomic Med*. 2019;7:e985. https://doi.org/10.1002/mgg3.985