The Egyptian Journal of Medical Human Genetics (2012) **13**, 257–262

Ain Shams University

The Egyptian Journal of Medical Human Genetics

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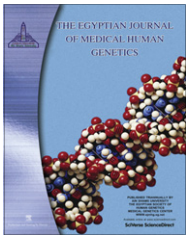

ORIGINAL ARTICLE

Association of the *UCP2* 45-bp insertion/deletion polymorphism with diabetes type 2 and obesity in Saudi population

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Received 24 March 2012; accepted 16 April 2012
Available online 19 May 2012

KEYWORDS

Diabetes type 2;
Obesity;
UCP2 gene;
Insertion/deletion polymorphism;
Saudi Arabia

Abstract Uncoupling protein-2 (UCP2) regulates insulin secretion and may play an important role in linking obesity to diabetes type 2 (T2D) that represents a major public health problem in Saudi Arabia. The present study aimed to evaluate the association between the 45-bp insertion/deletion (ins/del) in 3′UTR exon 8 within the *UCP2* gene as risk factors in T2D and obesity. This study assessed the body mass index (BMI) in 113 Saudi subjects (46 T2D, 38 obese and 29 healthy controls). The study genotyped for the *UCP2* ins/del polymorphism using polymerase chain reaction, evaluated its association with T2D and obesity, and compared its prevalence with those reported for other ethnic populations. The genotype frequencies were 63% for the del/del genotype, 32% for the ins/del genotype and 4% ins/ins genotype. The ANOVA between groups and within groups in T2D, obese, and healthy controls is non-significant ($p > 0.05$). The genotype distributions were figured in-between compared to those ethnic populations reported in the literature. Based on this Saudi study, the genetic variant UCP2 45-bp insertion/deletion do not influence T2D and obesity risks. These results were similar, but the insertion allele was modest relative to other ethnic populations.

1. Introduction

Uncoupling proteins (UCPs) are mitochondrial membrane transporters that disrupt the coupling between the mitochondrial proton gradient and ATP synthesis. UCP1 found in the inner mitochondrial membrane of brown adipose tissue, serves as a proton leak channel that allows cells to release stored energy as heat. While the physiological role of UCP1 in thermogenesis is relatively well understood, the function of its homologs, UCP2 and UCP3, remains unclear. UCP2 is widely distributed in human tissues (e.g. adipose tissue, skeletal muscle, heart,

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Peer review under responsibility of Ain Shams University.

Production and hosting by Elsevier

1110-8630
http://dx.doi.org/10.1016/j.ejmhg.2012.04.002

placenta, liver, kidney, pancreas, and brain). It has been shown that UCP2 plays neuromodulatory/neuroprotective roles in the CNS, and UCP3 protects neurons from glucose-induced degeneration by preventing reactive oxygen species (ROS) formation [1,2]. Indeed, superoxide or ROS production was increased in macrophages, pancreatic islets, or skeletal muscle mitochondria from UCP2-deficient mice, respectively [3,4]. Suggested models hypothesize roles for these genes in thermogenesis and body weight regulation, the reduction of mitochondrial ROS production, insulin regulation, and fatty acid export [5].

These recognized functions have justified the evaluation of common variants in these genes for a role in a variety of human diseases and phenotypes such as body composition and resting energy expenditure [6], energy metabolism [7], obesity [8,9], multiple sclerosis [10,11], diabetic neuropathy [12,13], coronary artery disease [14], and schizophrenia [15].

A genome scan performed at an average resolution of 8 cM, the most relevant logarithm of the odds (LODs) score peak in 11q13, lies about 8 cM from the UCP2 gene locus [16]. Taken together, it is apparent that the UCP2 gene is an excellent candidate for T2D. Many genetic polymorphisms have been identified in the UCP2 and UCP3 genes [17]. Of these, a 45-bp insertion/deletion polymorphism (rs1800795) in the 3′ untranslated region (3′UTR) of exon 8 in UCP2 has been studied in association with various pathological phenotypes [18]. The biological or functional relevance of both polymorphisms of UCPs has been previously shown. The UCP2 45-bp insertion/deletion polymorphism was reported to be related to metabolic rate [19] and increased BMI [6,20,21], whereas the UCP3 -55T allele was associated with increased expression of UCP3 mRNA in the skeletal muscle [22]. However, the patho-physiological impact of both polymorphisms remains unknown.

Thus, the present study evaluated the polymorphism of 45-bp insertion/deletion within the UCP2 gene as risk factors in diabetes type 2 and obesity using a case-control analysis in the Saudi population.

2. Subjects and methods

2.1. Participants

Both cases and controls were of Saudi origin and resident in the Western regions. For the sake of accuracy, we focused only on those subjects for whom specific clinical information was available. Cases were 113 selected from governmental and military hospitals in Western regions of Saudi Arabia. Permission to perform this study was obtained from the ethical committee of the Faculty of Applied Medical Sciences, King Abdul-Aziz University–Jeddah. Informed consents were taken from the cases. The present study comprised three groups: 46 subjects with T2D and 38 obese subjects. Patients with T2D were consecutively recruited who met the criteria of World Health Organization [23]: (1) diabetes diagnosed after 25 years, (2) insulin treatment not required for at least 2 years after diabetes diagnosis, and (3) absence of clinically evident autoimmune disease. We considered subjects as obese if their body mass indexes were (BMI) $\geqslant$ 30 kg/m^2 according to American Obesity Association [24]. In addition, age-matched healthy volunteers consist of 29 subjects who were randomly selected. Selection criteria of control group were as follows: fasting plasma glucose $<$6.1 mmol/L, no medications known to affect glucose and lipid metabolism, and absence of systemic diseases. They did not have a family history for T2D or obesity at first degree relative.

Table 1 Characteristics of phenotypic parameters: means of age and body mass index (BMI) ± SD.

Parameter	Age (years) (mean + SD)	BMI (kg/m^2) (mean + SD)	Female/male
T2D	27–67 (51.14 ± 9.98)	18–30 (25.3 ± 2.6)	16/30
Obesity	20–67 (32.3 ± 10.0)	30–65 (36.2 ± 5.55)	14/24
Healthy controls	20–66 (35.3 ± 9.0)	18–25 (23.02 ± 1.92)	10/19

Patients, who were under certain medication (e.g. cortisone) which could be the reason for their obesity, or could lead them to diabetes, were excluded from the study at time of sampling. In addition, patients who had endocrinal disorders that affected their weights (e.g. Cushing disease, hypothyroidism) and the female volunteers who had polycystic ovarian syndrome (PCOS) were also excluded. The average of ages and BMI of T2D, and obese patients, besides the healthy control group of the Saudi subjects ± standard deviations (SDs) are shown in Table 1.

2.2. DNA isolation

Genomic DNA was extracted from blood lymphocytes using a Spin Column miniKit (Qiagen, Valencia, CA).

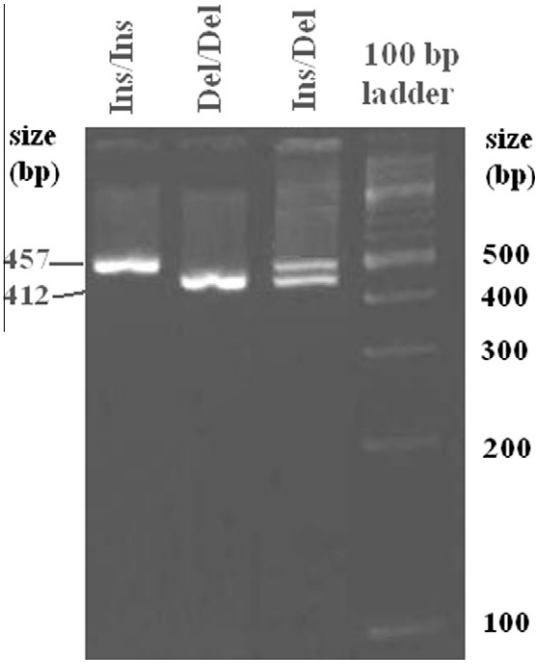

Figure 1 Gel patterns of UCP2 45-bp insertion/deletion polymorphism separated on 3% NuSieve gel. The homozygous Ins/Ins showed one PCR fragment of size 457 bp, and Del/Del showed a 412-bp fragment, while the heterozygous Ins/Del showed two fragments (457 plus 412 bp). MW is a 50 bp ladder.

2.3. Genotyping analysis

To amplify the 3′UTR exon 8 deletion (del)/insertion (ins) using polymerase chain reaction (PCR), genomic DNA (200 ng) was added to a 15-μl reaction mixture containing 0.5 μM of each primer with 200 μM of each dNTP's, 67 mM Tris–HCl, 16 mM $(NH_4)_2SO_4$, 0.01% Tween-20, 1 mM $MgCl_2$, and 0.45 U *Taq* DNA polymerase. Amplification conditions were 95 °C for 5 min followed by 35 cycles of 95 °C for 30 s, 65 °C for 40 s, 72 °C for 50 s. A final extension of 72 °C for 5 min was included.

Primer sequences were as forward, 5′-CAG TGA GGG AAG TGG GAG G-3′ and reverse, 5′-GGG GCA GGA CGA AGA TTC-3′ [19]. The amplified PCR product was resolved on 3% NuSieve agarose, visualized and photographed after staining with ethidium bromide using gel documentation system (Bio imaging system, SynGene, USA). Amplification of the *UCP2* del/ins resulted in 412-bp (Del) or 457-bp (Ins) fragments (Fig. 1).

2.4. Statistical analysis

Contingency tables were analyzed by Chi-square, continuous variables by ANOVA and *t*-test was used to determine if there is a difference between groups regarding the age and BMI (SPSS for Windows, version 16.0).

3. Results

We studied the impact of the UCP2 45-bp ins/del genotypes on prospective risk of T2D as well as the obesity among Saudi families. In the present study, among the random sample groups, the female/male gender ratio in T2D was 1:1.9, in obese subjects was 1:1.7, and in healthy controls was 1:1.9. The BMI reflected an informative shade on the Saudi sample group of T2D and obesity. In T2D Saudi subjects, the BMI frequency increased till reaching its maximum value at 24–29 and then decline at 30–31 kg/m^2. The obese curve started at a maximum BMI with 30–35 kg/m^2 and then collapsed at BMI with 56 and 65 kg/m^2 (Fig. 2).

With regard to genotype frequency of the *UCP2* 45-bp ins/del distribution in the present study, the ins/del was 32.6% in T2D and 31.6% in obese subjects, while the frequencies of the homozygous genotype ins/ins were 4.3% and 5.3% in T2D and obese subjects, respectively. The most frequent genotype in all Saudi sample groups, in this study, was the del/del genotype ranging from 63% to 65.5%. Table 2 disclosed that the differences between the genotypes in separate T2D, obese and control groups were statistically highly significant. The ANOVA statistical parameters between groups and within groups in T2D, obese, and healthy controls are shown in Table 3, with no significance ($p > 0.05$). As for the allele frequency of the insertion allele, the results were 20.7%, 21.1%, and 17.2% in T2D, obese subjects, and healthy controls, respectively.

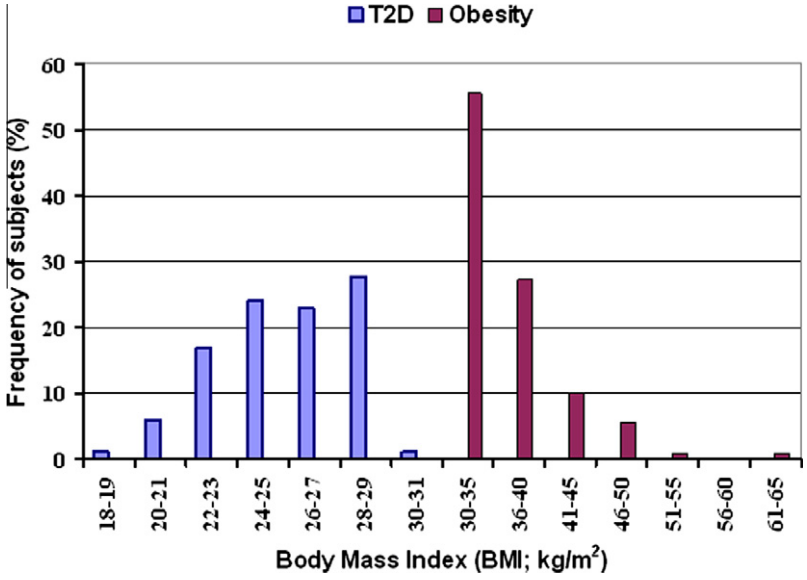

Figure 2 The body mass index (BMI), in the T2D and obese Saudi subjects.

Table 2 Genotype determining risk of UCP2 45-bp insertion/deletion among obesity, T2D and obese Saudi subjects.

Populations	Total subjects	Insertion/deletion genotypes *n* (%)			χ^2 Value	*p*-Value[a]	Insertion allele frequency
		Del/del (%)	Ins/del (%)	Ins/ins (%)			
Diabetic	46	29 (63.0)	15 (32.6)	2 (4.3)	23.8	< 0.0001	19/92 (0.21)
Obese	38	24 (63.2)	12 (31.6)	2 (5.3)	21.2	< 0.0001	16/76 (0.21)
Healthy control	29	19 (65.5)	10 (34.5)	0 (0.0)	11.7	0.002	10/58 (0.17)

[a] *p*-Values are considered as significant if it is $p < 0.05$.

Table 3 ANOVA statistical testing for the T2D, and obese Saudi sample group.

ANOVA	Degree of freedom (df)	*F*-test	*p*-Value*
T2D group versus control	2	0.764	0.476
Obese group versus control	2	0.846	0.441
T2D versus obese groups	2	1.928	0.161

* *p*-Values are considered significant if $p < 0.05$.

4. Discussion

Our diabetes mellitus is talented as a major public health trouble in Saudi Arabia in parallel with the worldwide diabetes pandemic, which is having a particular impact upon the Middle East and the third world [25,26]. This diabetes pandemic description has accompanied the adoption of a modern lifestyle and the abandonment of a traditional lifestyle, with a resultant increase in rates of obesity and other chronic noncommunicable diseases. The indigenous Saudi population seems to have a special genetic predisposition to develop T2D that further amplified by a rise in obesity rates, a high rate of consanguinity and the presence of other variables of the insulin resistance syndrome [27].

Not surprisingly, the discovery of the UCP1 homologs UCP2 [28] and UCP3 [29] in 1997 was warmly welcomed. The ubiquitous expression of UCP2, the expression of UCP3 in skeletal muscle, and their homology with the "true" [30] uncoupling protein UCP1 made UCP2 and UCP3 attractive targets for interventions aimed at manipulating energy expenditure. Extensive research toward the regulation and the supposed functions of these novel uncoupling proteins have resulted in a vast amount of publications in the last decade years [18].

Identification of candidate gene responsible for obesity is an impotent to understanding of molecular mechanisms not only for obesity, but also for obesity-related conditions, such as T2D. The discovery that UCP2 is present in pancreatic β-cells and adipose tissues has led to the suggestion that such molecules may be able to play an important role in etiology of obesity and T2D [31,32]. Many published papers have reported the association between −866G > A SNP in the promoter region of UCP2 with obesity and T2D [26,33–41].

Progressions have been achieved to clarify the important role of the mitochondrial UCP2 gene, and the association between the two common polymorphisms; the −866G > A SNP in the promoter region and 3′UTR ins/del of exon 8 and T2D, or obesity. Few studies have discussed the UCP2 45-bp ins/del polymorphism, but studies on the role of polymorphism in UCP2 45-bp ins/del as a risk factor for T2D and obesity have obtained controversial results [6,20,42,43].

There was a striking distribution of the *UCP2* ins/del polymorphism in the Saudi population as previously indicated. Table 4 compared the frequencies and observations of the UCP2 3′UTR exon 8 genotype in the present study with those published for other ethnic populations. The allele frequency of the insertion allele in T2D or obesity was 19/92 (21%) and of the deletion allele was 73/92 (79%). Evaluation of the Saudi frequency of the *UCP2* insertion allele (21%) in either T2D or obese subjects represented an intermediate magnitude with other ethnic groups that report frequencies ranging from 13% in type 2 diabetic Japanese requiring insulin treatment [44] to 33% in Pima Native Americans [19]. In this regard, Fig. 3 displayed the two extremes for the UCP2 45-bp insertion allele in both Tongans (a group of islands situated in the South Pacific), and Japanese [44]. Tongan and French populations reported the absence of the ins/ins genotypes. Duarte et al. [43] reported that the frequencies of the del/del and ins/del genotypes were 97% and 3%, with the absence of ins/ins genotype. They concluded that there was a unique, near-uniform distribution of the UCP2 45-bp ins/del polymorphism in Tongans as a result of a founder effect and may be relevant to the prevalence of obesity and T2D in Tonga. A French study of obese and control subjects by Otabe et al. [42] found a del/del frequency of 51% and 56% and ins/del of 49% and 44%, respectively, and no ins/ins genotype. Fig. 3 disclosed that the pattern of the UCP2 3′UTR ins/del genotypes in Saudi subjects was near-consistent with that reported in South Indians [20]. Though there was an effect due to the small sample size. This intermediacy might be due to the consequences of much social intermarriage of ethnic Saudi families with some Asians, and North Africa Arabs (Table 4).

Table 4 The heterozygous and homozygous 45-bp insertion allele within the 3′UTR–UCP2 gene in different ethnic populations.

Population (references)	Frequency (%)		Total (*n*)	Findings
	Ins/del	Ins/ins		
Obese Saudi Arabia	32	5	38	No association with obesity or T2D
T2D Saudi Arabia (this study)	33	4	46	
South Indians	28	5	453	Association of ins/ins genotype with increasing BMI in
British obese females [20]	42	5	83	South Indians and decrease of leptin in obese British females
Tongans [43]	3	0	1012	No association with obesity or T2D
Obese French Cauc.	49	0	483	No association with obesity or T2D
Control French Cauc. [42]	44	0	113	
Germans [21]	40	7	815	Association of ins-allele with obesity especially in elderly subjects
Obese Danish Cauc.	39	11	744	No association with obesity or T2D
Control Danish Cauc. [17]	42	9	872	
T2D Japanese	20	3	99	No association with obesity or T2D
Control Japanese [44]	32	5	120	
American children [6]	37	7	89	Association of ins/del with increasing BMI and increasing body fat
Pima Native Americans [19]	35	16	790	Association of ins/del with increasing SMR and decrease BMI

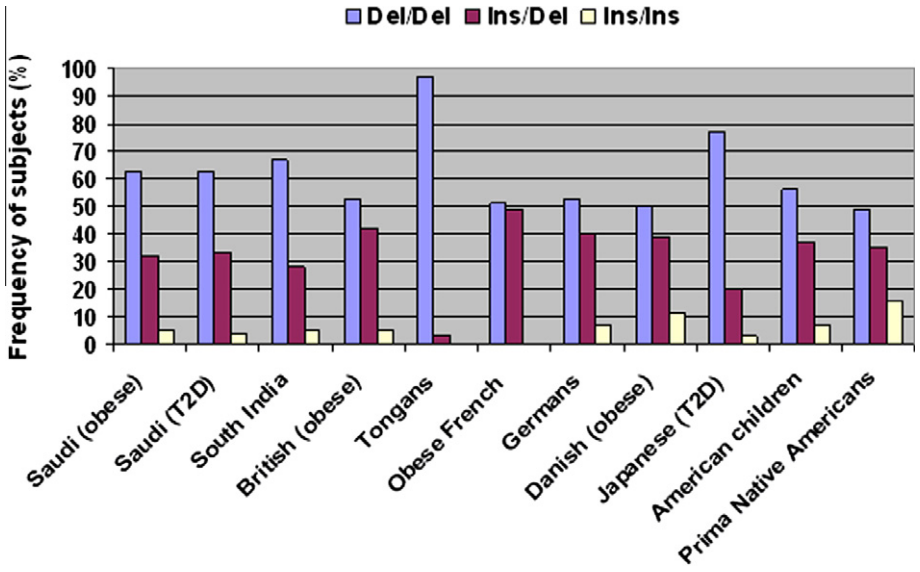

Figure 3 Comparison of the UCP2 45-bp insertion/deletion genotypes of T2D/obesity Saudi Arabia with different population.

In conclusion, the present study found that the *UCP2* 45-bp insertion/deletion polymorphism was not significantly associated with T2D or obesity in Saudi subjects, but the insertion allele is in a range of different ethnic populations. Our observations were in agreement with other previous reports, but sustain the need for replication of a cohort study of the UCP2 45-bp ins/del polymorphism among Type 2 diabetes and obesity. It is also possible that one or more of these variants in conjunction with other variants increases risk for T2D and obesity.

Acknowledgments

The author would like to express his deep appreciation to the Research Deanship at King Abdulaziz University–Jeddah, for the generous fund of the project (Grant #429/002-13).
He also would like to thank the families of diabetes and obesity for their willing to share this study.

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