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An uncoupling protein 3 gene polymorphism associated with a lower risk of developing Type II diabetes and with atherogenic lipid profile in a French cohort

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Abstract

Aims/hypothesis. The *UCP2-UCP3* gene region has been previously associated with obesity and diabetes. In a large representative cohort of Northern France (MONICA project), we studied the effect of a recently reported C/T polymorphism located in the 5' sequences of the *UCP3* gene on anthropometric measurements and lipid profile. We also examined the association of this polymorphism with obesity and Type II (non-insulin-dependent) diabetes mellitus.
Methods. The –55 C/T polymorphism of the *UCP3* gene has been genotyped in 1155 subjects from the MONICA project. Association studies were done with diabetes, obesity and related phenotypes. Results were ascertained in a second cohort of well-characterized Type II diabetic and control subjects.
Results. The variant T allele was associated with a decreased risk of developing Type II diabetes. Frequencies of the T allele were 13.3 % compared with 22 %, $p = 0.04$, in the diabetic and control groups, respectively. This observation was confirmed in the second cohort of French Type II diabetic ($n = 171$) and control ($n = 124$) subjects: 17.8 % compared with 25 %, $p = 0.03$. Moreover, subjects bearing the *TT* genotype had higher plasma total cholesterol and LDL-cholesterol concentrations ($p = 0.0006$ and $p = 0.001$, respectively) than subjects bearing wild or heterozygous genotypes.
Conclusion/interpretation. The *UCP3* –55 C/T polymorphism was associated with a higher atherogenic profile and modified the risk for the development of Type II diabetes. [Diabetologia (2000) 43: 1424–1428]

Keywords Uncoupling protein (UCP), polymorphism, Type II diabetes, obesity.

Uncoupling proteins (UCPs) constitute a family of intramitochondrial transmembrane carrier proteins [1]. They function to dissipate proton gradients and to uncouple respiration from oxidative phosphorylation, thus converting fuel to heat. Confined to brown adipose tissue *UCP1* is unlikely to play a major part in energy expenditure in humans [2]. The *UCP2* gene is widely expressed, especially in skeletal muscle and white adipose tissue [3], whereas *UCP3* is predominantly expressed in skeletal muscle, a tissue contributing to thermogenesis in humans [4, 5]. The *UCP3* gene is located within 7 kb of *UCP2* on the human chromosome 11q13 [6]. Both are candidate genes for the regulation of human energy metabolism and thus obesity. Genetic markers close to the *UCP2*/*UCP3* locus are linked to resting metabolic rate (RMR) in humans [7], reinforcing the previous hypothesis. Moreover, quantitative trait loci (QTL) linked to obesity and Type II (non-insulin-dependent) diabetes mellitus have been described on the mouse region of chromosome 7 syntenic to human 11q13 [8, 9]. An association between polymorphisms of the *UCP3* gene and Type II diabetes has been described in a French morbidly obese cohort [10]. Vari-

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Abbreviations: UCP: Uncoupling protein, QTL: quantitative trait locus, PPAR: peroxisome proliferator-activated receptor, HOMA: homeostasis model assessment.

Table 1. Genotype and allele distributions of the *UCP3* –55 C/T polymorphism in the MONICA cohort

	Non-obese non diabetic subjects	Obese subjects	Type II diabetic subjects
n	894	232	49
Age (years)	51 ± 8	53 ± 8	56 ± 7
Men, %	52	45	47
BMI, kg/m^2	24.6 ± 2.9	34.4 ± 4.0	31.5 ± 6.6
range	16–29	30–57	21–57
Glucose, mmol/l	5.25 ± 0.89	6.44 ± 2.40	9.36 ± 3.40
Insulin, μU/ml	13.78 ± 8.05	24.59 ± 14.77	23.26 ± 11.26
CC, *n* (%)	542 (60.6)	143 (61.6)	36 (73.5)
CT, *n* (%)	312 (34.9)	78 (33.6)	13 (26.5)
TT, *n* (%)	40 (4.5)	11 (4.8)	0 (0)[a]
C allele, *n* (%)	1396 (78.0)	364 (78.4)	85 (86.7)
T allele, *n* (%)	392 (22.0)	100 (21.6)	13 (13.3)[b]

[a] Type II diabetic vs control subjects $p = 0.12$ (Fisher exact test).
[b] Type II diabetic vs control subjects, $p = 0.04$ ($\chi^2 = 4.13$)

ations of the *UCP3* gene expression have been reported in patients with Type II diabetes, suggesting a potential causal role of the *UCP3* gene in this complex trait [11–13]. A C/T polymorphism in the *UCP3* gene, located at position –55 according to the beginning of exon 1 [14] is associated with an increase in *UCP3* mRNA expression in male non-diabetic Pima Indians [15]. Therefore, we tested the effect of this polymorphism on obesity, lipid variables and Type II diabetes in two independent cohorts: 1155 subjects from the MONICA cohort representative of Northern France and a Type II diabetes case-control study (171 patients/124 control subjects) whose participants were selected from a well-characterized collection of French subjects [16].

Subjects and methods

The first cohort studied was selected between 1995 and 1997 from a large representative French sample who were aged 35 to 65 years and participated in the risk factor surveys of the WHO-MONICA project (World Health Organization Multinational monitoring of trends and determinants of cardiovascular diseases) [17–19]. The ethics committee of the Central Hospital and University of Lille approved the study. Each subject signed a form giving informed consent. A total of 1155 DNA samples could be obtained. From this sample, 232 subjects were obese (BMI > 30 kg/m^2), 49 suffered from Type II diabetes, identified on the basis of a medical diagnosis and on the existence of a specific treatment and 894 were neither diabetic nor obese. To avoid possible interferences of treatments on blood variables, we excluded subjects receiving medical treatment for diabetes, hypercholesterolaemia or hypertension from the statistical analyses, resulting in a sample size of 834 subjects (116 obese and 718 non-obese subjects).

For case-control studies, unrelated Type II diabetic ($n = 171$, age = 56 ± 7 years, BMI = 28.1 ± 4.8 kg/m^2) and control subjects ($n = 124$, age = 54 ± 7 years, BMI = 23.1 ± 2.4 kg/m^2) subjects aged from 35 to 65 years were selected from a well-described French collection [16]. Genomic DNA was extracted from leucocytes as described previously [20]. Typing of the *UCP3* –55 C/T was achieved as described previously [14]. Insulin resistance (IR) was assessed with the homeostasis model assessment (HOMA) [21]. Statistical analyses were done with the SAS statistical software, version 6.12 (SAS Institute, Cary, N.C., USA). Genotype and allele distributions were compared with Pearson chi-squared or Fisher exact tests. The effect of the polymorphism on the disease was tested in a multiple logistic regression model adjusted for age, sex, body mass index and estimated by the odds ratio, an approximation of the relative risk in case-control studies. The effect of the polymorphism on quantitative variables was tested with a multivariate analysis of covariance using a general linear model. Data for triglycerides, insulin, and glucose were log-transformed to normalize the distributions. Interactions between genotypes and covariates were tested. We considered differences significant at p less than 0.05.

Results

In non-obese, non-diabetic subjects ($n = 894$), 60.6% were *CC*, 34.9% were *CT* and 4.5% were *TT* (Table 1). The –55 T allele frequency was 22% and the genotype distribution did not statistically significantly differ from the Hardy-Weinberg equilibrium expectation. Allele frequencies were similar in the obese subjects ($n = 232$, BMI > 30 kg/m^2, mean BMI = 34.4 ± 4.0 kg/m^2, T allele frequency = 21.6%). The T allele was, however, less frequent in the Type II diabetic subjects ($n = 49$, BMI = 31.5 ± 6.6 kg/m^2) than in the non-obese, non-diabetic control subjects: 13.3% compared with 22.0%, $p = 0.04$. We then explored the quantitative effect of the *UCP3* C/T polymorphism on the variation of body mass index and lipid variables in subjects without any treatment for diabetes, hypercholesterolaemia or hypertension ($n = 834$, BMI = 25.5 ± 4.3 kg/m^2) (Table 2). The genotype and allele distributions of the C/T polymorphism did not differ from those reported for non-obese, non-diabetic subjects. Homozygote *TT* subjects had higher plasma cholesterol (~ + 10%, $p = 0.0006$), LDL-cholesterol (~ + 18%, $p = 0.001$) and apolipoprotein concentrations (~ + 14%, $p = 0.0001$) than C allele carriers. This effect was con-

Table 2. Effect of the *UCP3* –55 C/T polymorphism in the MONICA cohort

	CC	*CT*	*TT*	*p* (*CC* + *CT* vs *TT*)
n	518	281	35	
BMI, kg/m^2[a]	25.8 ± 4.4	25.5 ± 4.7	25.7 ± 3.7	0.91
Glucose, mmol/l[b]	5.25 ± 0.78	5.23 ± 1.04	5.28 ± 1.00	0.34
Insulin, μU/ml[b]	14.85 ± 10.24	13.95 ± 7.74	14.71 ± 6.21	0.93
Triglycerides, mmol/l[b]	1.09 (0.63–1.90)	1.10 (0.60–2.03)	1.10 (0.71–1.72)	0.65
Cholesterol, mmol/l[b]	5.83 ± 1.03	5.74 ± 1.00	6.39 ± 1.15	0.0006
HDL chol., mmol/l[b]	1.52 ± 0.48	1.53 ± 0.49	1.48 ± 0.45	0.46
Apo A-I, g/l[b]	1.73 ± 0.32	1.72 ± 0.33	1.73 ± 0.31	0.99
LDL chol., mmol/l[b]	3.74 ± 0.98	3.62 ± 0.97	4.38 ± 1.16	0.0011
Apo B, g/l[b]	1.18 ± 0.28	1.16 ± 0.29	1.33 ± 0.33	0.0001

Data are means ± SD. [a] *p* value adjusted for age, sex, alcohol and smoking consumption. [b] *p* values adjusted for age, sex, body mass index, alcohol and smoking consumption. Apo = apolipoprotein, chol = cholesterol

Table 3. Genotype and allele distributions of the *UCP3* –55 C/T polymorphism in the Type II diabetes case-control study

	Control subjects (*n* = 124)	Type II diabetic subjects (*n* = 171)
Age (years)	54 ± 7	56 ± 7
BMI, kg/m^2	23.1 ± 2.4	28.1 ± 4.8
Insulin, μU/ml	8.48 ± 5.43	12.68 ± 9.84
Glucose, mmol/l	5.09 ± 0.50	10.27 ± 3.93
CC, *n* (%)	70 (56.5)	116 (67.8)
CT, *n* (%)	46 (37.1)	49 (28.7)
TT, *n* (%)	8 (6.4)	6 (3.5)[a]
C allele, *n* (%)	186 (75.0)	281 (82.2)
T allele, *n* (%)	62 (25.0)	61 (17.8)[b]

[a] Type II diabetic vs control subjects, $p = 0.11$ ($\chi^2 = 4.38$).
[b] Type II diabetic vs control subjects, $p = 0.03$ ($\chi^2 = 4.47$).
OR = 0.50 (0.26–0.96), $p = 0.04$ (adjusted for age, sex and BMI) for *CC* vs *CT* + *TT* subjects

sistent in both sexes (data not shown). In contrast, no differences between the two groups of genotypes could be detected for body mass index, other anthropometric measurements (waist to hip ratio and waist circumference) or for fasting plasma glucose, insulin concentrations and the insulin resistance index (data not shown) as measured by the homeostasis model assessment (HOMA). No statistically significant associations with these phenotypes were detected in the subgroup of obese subjects ($n = 116$).

We analysed the distribution of the *UCP3* C/T polymorphism in a French case-control study composed of 171 well-characterized patients suffering from Type II diabetes and 124 control subjects. As in the MONICA cohort, the –55 T allele was less frequent in the Type II diabetic than in the control subjects: 17.8 % compared with 25 %, $p = 0.03$, odds ratio 0.50 [0.26–0.96], $p = 0.038$ for *CC* compared with *CT* + *TT* subjects (adjusted for age, sex, body mass index) (Table 3). No difference between the genotypes was detected for the HOMA insulin resistance index.

Discussion

Our data support the hypothesis of an association between the –55 C/T polymorphism of the *UCP3* gene and Type II diabetes in French Caucasians. Importantly, these results were found in two independent cohorts (one representative of the general population from the North of France, the second one with diabetic subjects from all parts of France with a strong family history of diabetes and their spouses as control subjects). We found subjects bearing the *TT* genotype of the *UCP3* –55 C/T polymorphism have a lower risk for developing Type II diabetes than others do. Previous reports, although conflicting, suggest an alteration of skeletal muscle *UCP3* gene expression in Type II diabetic patients [11–13] suggesting that *UCP3* regulation plays a part in the development of this disease. Furthermore, several groups reported that the *UCP2-UCP3* locus could be genetically linked to the variation of different quantitative traits associated with diabetes and insulin resistance in animals and in humans: hyperinsulinaemia in mice [3], metabolic rate in young non-diabetic Pima Indians [22] and 2-h insulin concentrations during an oral glucose tolerance test in prediabetic Pima Indians [23]. Increased non-esterified fatty acid concentrations induce a noticeable increase in skeletal muscle *UCP3* and not *UCP2* gene expression in humans [24] and in rats [25]. If long-term weight loss is associated with a down-regulation of UCP3 in humans [26] in agreement with an increased metabolic efficiency in these conditions [27], *UCP3* expression is increased during short-term fasting in human and rodent muscle [28–31], a condition characterized by fatty acid release from body fat stores, due to increased lipolysis [32]. The expression of *UCP3* seems to better correlate with fatty acid metabolism than with metabolic efficiency [33]. The increase in *UCP3* gene expression could constitute a compensatory mechanism to use NEFA as a fuel during the fasting state. It is noteworthy that the role of UCP3 as a conventional uncoupling protein dissipating energy in heat (like

UCP1) is questionable [34]. High NEFA concentrations do not affect basal glucose-stimulated insulin secretion [35] but are well known to predispose to insulin resistance [36, 37]. The –55 C/T *UCP3* polymorphism has been associated with increased skeletal muscle expression of UCP3 in non-diabetic Pima Indians [15], thus we hypothesize that increased expression of *UCP3* from the variant T allele has a protective effect against insulin resistance through NEFA metabolism. The suppression of NEFA induction of *UCP3* expression by hyperinsulinaemia [24] could be considered as one of the elements of a vicious circle in Type II diabetes progression. Unfortunately NEFA concentrations were not available in our cohorts and indirect testing of insulin resistance through the homeostasis model remained insignificant.

Our results suggest an effect of the human *UCP3* gene on serum lipid concentrations and the atherogenic profile. It is notable that in the MONICA cohort, subjects carrying the *TT* genotype had a more atherogenic lipid profile characterized by statistically significant higher plasma total cholesterol, higher LDL-cholesterol and apolipoprotein B concentrations than subjects with other genotypes did. These associations were consistent in men and women, suggesting there was no sex effect of the *UCP3* polymorphism. Among the numerous genes involved in lipoprotein metabolism those coding for the peroxisome proliferator-activated receptors (PPARs) and particularly PPAR gamma seem of relevance [38]. The latter is activated by thiazolidinediones [39], reagents known to improve insulin sensitivity, but that could also contribute to dyslipidaemia [40, 41]. In rat the *UCP3* gene expression is enhanced by thiazolidinediones [42] and the human *UCP3* gene promoter contains putative peroxisome proliferator responsive elements [43]. The location of the *UCP3* C/T polymorphism is still debated: originally mapped near the TATA box in the promoter region (–55), a recently published alternative *UCP3* genomic organization [43] locates the variant in the 5' UTR at position + 527. These discrepancies make potential functional studies more problematic. In the recently published organization [43], the –55C/T polymorphism is located 4 bp downstream a putative PPAR responsive element and thus could modify the PPAR responsiveness of the *UCP3* gene. This gene could be one of the PPAR gamma targets involved in the modulation of insulin sensitivity and lipid metabolism.

Of note, we previously found that the *UCP3 TT* homozygous genotype was associated with a higher body mass index in morbidly obese subjects as well as in non-obese control subjects [14]. In the present report, the same *UCP3* promoter allele seems to protect against diabetes. This apparent paradoxal effect could be explained by interaction between UCP3 and PPARs. It was recently shown that a reduced PPAR gamma activity was associated with a resistance to diet-induced obesity in mice [44] as well as with Type II diabetes in humans [45]. In contrast, weight gain is a frequent side effect of thiazolidinediones. If UCP3 is a major PPAR target, it could be speculated that an increase in *UCP3* promoter activity could also protect against diabetes while mildly contributing to fat accumulation, which corresponds to our past and current finding.

We do not exclude the –55 C/T polymorphism being in linkage disequilibrium with another functional mutation in the *UCP2-UCP3* gene cluster. Association between *UCP2* polymorphisms and Type II diabetes was recently shown in the very insulin resistant Indian cohort [46]. Altogether, our present data reinforces previous studies suggesting a putative role of this locus on chromosome 11 q in the genetic risk for the metabolic syndrome.

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