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Dietary saturated fat, gender and genetic variation at the *TCF7L2* locus predict the development of metabolic syndrome☆

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Abstract

Transcription factor 7-like 2 (*TCF7L2*) is the strongest genetic determinant of type 2 diabetes (T2DM) and insulin-related phenotypes to date. Dietary fat is a key environmental factor which may interact with genotype to affect risk of metabolic syndrome (MetS) and T2DM. This study investigated the relationship between the *TCF7L2* rs7903146 polymorphism, insulin sensitivity/resistance and MetS in the LIPGENE-SU.VI.MAX study of MetS cases and matched controls (n=1754) and determined potential interactions with dietary fat intake. Female minor T allele carriers of rs7903146 had increased MetS risk (odds ratio [OR] 1.66, confidence interval [CI] 1.02–2.70, P=.04) and displayed elevated insulin concentrations (P=.005), impaired insulin sensitivity (P=.011), increased abdominal obesity (P=.008) and body mass index (P=.001) and higher blood pressure (P<.05) compared to the CC homozygotes. Metabolic syndrome risk was also modulated by dietary saturated fat (SFA) intake (P=.035 for interaction). High dietary SFA intake (≥15.5% energy) exacerbated MetS risk (OR 2.35, 95% CI 1.29–4.27, P=.005) and was associated with further impaired insulin sensitivity in the T allele carriers relative to the CC homozygotes (P=.025) and particularly to the T allele carriers with the lowest SFA intake (P=.008). No significant genotype effect on MetS risk or insulin sensitivity was evident among low-SFA consumers. In conclusion, the *TCF7L2* rs7903146 polymorphism influences MetS risk, which is augmented by both gender and dietary SFA intake, suggesting novel gene–diet–gender interactions.

Keywords: *TCF7L2*; Metabolic syndrome; Insulin sensitivity; Saturated fat; Gene–diet interaction; LIPGENE

1. Introduction

Metabolic syndrome (MetS) is a common, multicomponent condition characterized by insulin resistance, dyslipidemia, abdominal obesity and hypertension that is associated with an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease and atherosclerosis [1]. The current global epidemic in the incidence of MetS and T2DM is an important illustration of the interaction between environmental and genetic factors in diet-related polygenic disorders. With the advent of high-throughput genetic analysis, our understanding of the genetic architecture of diet-related polygenic disorders is improving. Two genome-wide association studies recently identified novel single nucleotide polymorphisms (SNPs) in the Wnt signalling regulated transcription factor 7-like 2 (*TCF7L2*) gene which are associated with increased T2DM risk [2,3], most likely through defective beta-cell function and impaired insulin secretion [2]. Several large studies subsequently replicated and confirmed the association with T2DM risk in various populations, and the *TCF7L2* rs7903146 SNP has emerged as one of the most important T2DM susceptibility gene variants known to date [4–9]. *TCF7L2* polymorphisms have also been associated with MetS components such as dyslipidemia and waist circumference [10,11]. However, prospective and population-based MetS association studies have produced conflicting results, with some reporting an association with MetS,

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GEE, generalized estimating equation; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; MUFA, monounsaturated fatty acid; NEFA, nonesterified fatty acid; PUFA, polyunsaturated fatty acid; QUICKI, quantitative insulin-sensitivity check index; SFA, saturated fatty acid; SNP, single nucleotide polymorphism; SBP, systolic blood pressure; TAG, triacylglycerol; *TCF7L2*, Transcription factor 7-like 2; T2DM, type 2 diabetes mellitus.

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hyperglycemia, impaired insulin secretion and hypertriglyceridemia [11,12], whilst others found no association with MetS or insulin resistance [13,14].

Data from the Diabetes Prevention Program and the Diabetes Prevention Study indicate that lifestyle or environmental factors can modulate the genetic effects of *TCF7L2* polymorphisms [2,9]. Dietary fat is an important environmental factor, wherein excessive exposure plays a key role in the development of MetS [15–20]. In terms of compositional effects, epidemiological and cohort studies suggest detrimental effects of saturated fat (SFA) on insulin sensitivity, promoting the development of diabetes [19,21,22]. Intervention and observational studies have shown that replacing SFA with monounsaturated fat (MUFA) may improve insulin sensitivity [23,24]. However, results of intervention trials to confirm these functional effects are mixed [25–27], perhaps reflecting genetic heterogeneity and interaction with dietary fat exposure [16,17]. A recent study demonstrated that dietary polyunsaturated fat (PUFA) modulated the genetic effects of the *TCF7L2* rs7903146 polymorphism on postprandial lipemia [11]. However, whether dietary fat could modulate the genetic association with *TCF7L2* rs7903146 within the context of MetS has not been explored. Therefore, the aim of this case–control study was to examine the relationship between the *TCF7L2* rs7903146 polymorphism on MetS risk and to investigate whether dietary fat composition modulated these associations.

2. Methods

2.1. Participants, MetS classification and study design

This study is part of a prospective case–control candidate gene study of LIPGENE, an EU Sixth Framework Programme Integrated Project entitled "Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis." Participants were selected from an existing French SU.VI.MAX cohort including 13,000 individuals studied over 7.5 years beginning in 1994 to 2002 [28]. The LIPGENE-SU.VI.MAX study is a nested case–control study of MetS consisting of women aged 35–60 years and men aged 45–60 years recruited from SU.VI.MAX. Additional ethical approval from the ethical committee (CCPPRB of Paris-Cochin Hospital) included an additional clause (n° Am 2840-12-706) to perform the biochemical analysis and genetic analysis required for the LIPGENE study. LIPGENE participants were informed of the study objectives and signed a consent form. Participants were invited to provide a 24-h dietary record every 2 months, for a total of six records per year. Information was collected with the use of computerized questionnaires that were transmitted during a brief telephone connection via the Minitel Telematic Network (France Télécom, Paris, France), a small terminal that was widely used in France as an adjunct to the telephone. Participants were guided by the software's interactive facilities and by a previously validated instruction manual for coding food portions that included more than 250 foods presented in three different portion sizes. Two intermediate and extreme portions could also be chosen, yielding a total of seven choices for estimating quantities consumed [29]. Baseline daily dietary intake data were estimated by using food composition tables validated for the French population [30].

Baseline and 7.5-year follow-up data including full clinical examination records were made available to LIPGENE. These data were used to identify cases, individuals who developed elements of MetS, over the 7.5-year follow-up period and control participants. Metabolic syndrome cases were selected according to screening criteria and a scoring system based on the National Cholesterol Education Program Adult Treatment Panel III criteria for the MetS [31]. Metabolic syndrome cases were required to fulfil at least three of the following five criteria: elevated waist circumference (>94 cm [men] or >80 cm [women]), elevated fasting blood glucose (≥5.5 mmol/L or treatment for diabetes), elevated triacylglycerol (TAG) (≥1.5 mmol/L or treatment for dyslipidemia), low high-density lipoprotein cholesterol (HDL-c) (<1.04 mmol/L [men] or <1.29 mmol/L [women]) and elevated systolic/diastolic blood pressure (SBP/DBP) (≥130/85 mmHg or antihypertensive treatment). Cases were defined as both men and women with at least three abnormalities, and controls were defined as men and women with no abnormalities or men with no more than one abnormality. Cases and controls (n=1754) were matched according to age (±5 years), gender and number of dietary records available.

2.2. Biochemical analysis

Fasting glucose, TAG, HDL-c and total cholesterol were measured as previously described [28]. Insulin and C-peptide were determined by electrochemiluminescence immunoassays (Roche Diagnostics, France). Nonesterified fatty acids (NEFA) and low-density lipoprotein cholesterol were measured by enzymatic colorimetric methods (Randox Laboratories, UK, and Roche Diagnostics, France). Homeostasis model assessment (HOMA-IR), a measure of insulin resistance, was calculated as [(fasting plasma glucose×fasting serum insulin)/22.5] [32]. Quantitative insulin-sensitivity check index (QUICKI), a measure of insulin sensitivity, was calculated as [1/(log fasting insulin+log fasting glucose+log fasting NEFA)] [33].

2.3. DNA extraction and genotyping

DNA extraction from buffy coats and whole genome amplification of low-yielding samples (<10 ng) were performed as previously described [34]. Genotyping for rs7903146 was conducted by KBiosciences (Herts, UK) using a competitive allele specific polymerase chain reaction system (KASPar). Genotype data were then uploaded into HITAGENE, a Web-based combined database and genetic analysis software suite developed by Hitachi Dublin Laboratory. A genotype success rate of 99% and call rate of 99% were achieved.

2.4. Statistical analysis

Statistical analysis was performed using SAS for Windows, version 9.0 (SAS Institute, USA). Data are expressed as means±S.E. After checking for skewness and kurtosis, glucose, insulin, NEFA, TAG, QUICKI and HOMA-IR were normalized by logarithmic transformation. Departure of genotype distributions from Hardy–Weinberg equilibrium was assessed using χ^2 tests in HITAGENE. Genotype frequencies were compared between cases and controls in HITAGENE using Fisher's Exact Test. Logistic regression was used to determine associations between genotype and MetS, and interaction between genotype, dietary fat and MetS risk. The generalized estimating equation (GEE) linear regression [35] investigated associations between genotype and continuous phenotypes. Analyses were performed on the whole study population and then stratified by gender to ascertain the homogeneity of genetic effects. Three genotype groups were first considered to check different inherent models. Where a dominant or recessive effect existed, analysis was repeated comparing carriers vs. noncarriers of that particular allele. To further determine modulation by fatty acids, association analyses were repeated using the median dietary intake of control participants to dichotomize dietary fatty acids. Where gene–diet interactions were identified, formal tests of heterogeneity (Breslow–Day) between the odds ratios (ORs) of the stratum-specific estimates were performed. Potential confounding factors used in the adjusted multivariate analysis included age, gender, body mass index (BMI), smoking status, physical activity, energy intake and use of medications including lipid-lowering, hypertension and diabetes treatments. A P value of <.05 was considered as significant.

3. Results

3.1. Association between TCF7L2 rs7903146 and MetS

Genotype distributions did not deviate from Hardy–Weinberg equilibrium (P>.01). In the adjusted multivariate model, rs7903146 displayed a genotype effect on MetS risk (P=.03), particularly under the dominant model when the T allele carriers were compared to the CC homozygotes (OR 1.54, confidence interval [CI] 1.11–2.14, P=.01). Homogeneity of this genetic effect was assessed by stratifying according to gender. The association with MetS was gender specific, with the deleterious effects of rs7903146 T allele deriving from the female participants (OR 1.66, CI 1.02–2.70, P=.04); although the effect was in the same direction in the male participants, it did not reach statistical significance (P=.09).

3.2. Clinical characteristics and dietary fat intake according to genotype

As expected, more MetS cases were in possession of a T allele compared to the CC homozygotes (Table 1). Age and gender distribution was not different between groups. In terms of their phenotype, the T allele carriers had higher plasma insulin concentrations, displayed impaired insulin sensitivity (QUICKI) and were more insulin resistant (HOMA) relative to the CC homozygotes. T allele carriers also had greater waist circumference and BMI, in addition to higher systolic and diastolic blood pressure, compared to the CC homozygotes. None of the lipid-related variables were different between genotypes (data not shown). Total dietary fat intake, or SFA, MUFA or PUFA components were not different between genotypes. As gender differences were noted in the genetic analysis, we analyzed the clinical characteristics and dietary fat intake according to both genotype and gender (data not

Table 1
Clinical characteristics and dietary fat intake according to *TCF7L2* rs7903146 genotype among all individuals

	TT	CT	CC	CT+TT
n	192	772	790	964
Case/control %	52/48*	52/48*	45/55	52/48*
Male/female n	104/88	479/293	474/316	583/381
Age, years	58.01±0.19	58.37±0.19	57.98±0.40	58±0.19
Plasma insulin, pmol/L	52.30±1.53*	51.95±1.50*	45.42±1.45	52.05±1.50*
Plasma glucose, mmol/L	5.24±0.04	5.29±0.04	5.17±0.06	5.26±0.04
HOMA-IR	1.85±0.07**	1.86±0.07**	1.57±0.11	1.86±0.07**
QUICKI	0.30±0.00*	0.30±0.00*	0.32±0.01	0.30±0.00**
BMI, kg/m^2	26.2±0.32***	26.1±0.16***	25.0±0.17	26.1±0.16***
Waist, cm	89±0.99***	89±0.47***	85±0.48	89±0.47***
SBP, mm Hg	131±1.29	131±1.28*	129±1.55	131±0.57*
DBP, mm Hg	82±0.71*	83±0.35*	80±0.33	82±0.34**
Dietary fat (% energy)	35.25±0.27	35.54±0.27	34.98±0.26	35.35±0.27
SFA (% energy)	15.34±0.30	15.57±0.14	15.27±0.30	15.42±0.14
PUFA (% energy)	5.74±0.17	5.63±0.08	5.61±0.08	5.64±0.10
MUFA (energy)	14.24±0.25	14.35±0.13	14.08±0.13	14.28±0.17

Values are means±S.E.M. Generalized estimating equation linear regression was performed to identify significant differences between *TCF7L2* rs7903146 genotypes in all participants after adjustment for potential confounding factors including age, gender, BMI, smoking status, energy intake, physical activity and medication use.
*P<.05; **P<.01; ***P<.005 compared to the CC homozygotes.

shown). Not surprisingly, the female T allele carriers also had higher plasma insulin concentrations (P=.005), reduced insulin sensitivity (P=.011) and higher waist circumference (P=.008), BMI (P=.001) and systolic blood pressure (P=.031) relative to the CC homozygotes. Total fat intake was not different between genotypes, but PUFA intake was higher in the female CC homozygotes (P=.042). In males, none of the lipid- or insulin-sensitivity-related variables were different between genotypes.

3.3. Dietary fat intake modulates genetic predisposition to MetS

We investigated whether dietary fatty acid composition altered the association with MetS risk by performing logistic regression analyses below and above the control median of dietary fatty acid intake. Interestingly, high dietary SFA intake (≥15.5% of energy) exacerbated the genetic susceptibility to MetS (Table 2). Interaction analysis confirmed this gene–diet interaction (P=.035). When dietary fatty acid intake was stratified according to control median intake, among all individuals with high dietary SFA intake, the minor T allele carriers of rs7903146 had further increased MetS risk (OR 2.35) compared to their respective major C allele homozygotes. However, among individuals with low dietary SFA intake (<15.5% of energy), the increased MetS risk conferred by this SNP was not observed. Formal tests of heterogeneity (Breslow–Day) between the ORs of the stratum-specific analysis substantiated this gene–diet interaction (P=.042).

We examined the influence of the other dietary fat components on MetS risk (Table 2). Low PUFA intake (<5.54% of energy) was associated with a further increase in MetS risk in the minor T allele carriers of rs7903146, and when dietary PUFA intake was high (>5.54% of energy), the increased MetS risk conferred by the rs7903146 T allele was not present. Individual PUFA components were analyzed to ascertain if particular PUFA classes were responsible for this effect. Similar results were obtained for each of the PUFA constituents ([n-6], [n-3] and LC [n-3] PUFA). When dietary MUFA intake was analyzed, low MUFA intake (<14% of energy) also had a modest influence on MetS risk in the T allele carriers of rs7903146 compared to the CC homozygotes. It should be noted however that formal tests of heterogeneity between the ORs of these stratum-specific estimates failed to reach significance.

Table 2
Odds ratios for the association between *TCF7L2* rs7903146 and MetS according to dietary fat intake and composition

Median % energy	OR (95% CI) for MetS stratified according to dietary fat median intake (T allele carriers v CC homozygotes)				Test for heterogeneity
	Above fatty acid median	*P* value	Below fatty acid median	*P* value	*P* value
SFA (15.5%)	2.35, CI 1.29–4.27	.005	1.26, CI 0.85–1.90	.247	.042
Total PUFA (5.54%)	1.34, CI 0.76–2.34	.312	1.65, CI 1.11–2.49	.016	.403
(n-6) PUFA (4.97%)	1.41, CI 0.76–2.62	.277	1.57, CI 1.06–2.32	.023	.476
(n-3) PUFA (0.56%)	1.25, CI 0.66–2.37	.487	1.64, CI 1.11–2.40	.012	.555
LC (n-3) PUFA (0.17%)	1.25, CI 0.63–2.50	.521	1.63, CI 1.20–2.33	.013	.448
MUFA (14%)	1.33, CI 0.76–2.31	.322	1.65, CI 1.09–2.49	.017	.781

Values represent OR (95% CI) for MetS for T allele carriers (CT+TT) compared to the CC homozygotes within each dietary fat strata. *P* values were calculated by logistic regression adjusting for potential confounding factors including age, gender, BMI, smoking status, physical activity, energy intake and use of medications including lipid-lowering, hypertension and diabetes treatments. *P* values for the tests of heterogeneity between the ORs of the stratum-specific estimates were calculated by the Breslow–Day test.

3.4. Gene–diet interactions influence insulin sensitivity

As insulin sensitivity was significantly different between the T allele carriers and the CC homozygotes, we additionally investigated the impact of dietary SFA intake and genotype on insulin related phenotypes (Fig. 1). Interestingly, among the high SFA consumers, insulin sensitivity was further impaired in the T allele carriers relative to the CC homozygotes (P=.025) and particularly to the T allele carriers with the lowest SFA intake (P=.008) (P=.025 for interaction). Similarly, plasma insulin, but not glucose, concentrations were higher in the T allele carriers relative to the CC homozygotes with the highest SFA intake (P=.03) (P=.042 for interaction). It was also interesting to note that genotype did not affect any of these insulin-related phenotypes among individuals who habitually consumed a low SFA diet. Interaction analysis confirmed the gene–diet interaction effects on insulin sensitivity and plasma insulin concentrations (global P<.05).

4. Discussion

In this study, we demonstrated that a common genetic variant at the *TCF7L2* locus, rs7903146, was associated with increased MetS risk, arising from their impaired insulin sensitivity, greater insulin resistance, increased abdominal obesity and hypertension. These associations derived from the female participants. Dietary fat intake, recorded 7.5 years prior to MetS case/control selection, modulated the genetic influence on MetS risk. In particular, high dietary SFA intake (≥15.5% of energy) accentuated the deleterious effects of rs7903146 on MetS risk, suggesting that the long-term effect of dietary fatty acid composition and consumption may have the potential to modify the genetic susceptibility of developing the disease.

While the association between *TCF7L2* polymorphisms and type 2 diabetes risk has been widely replicated in various populations [4,9], associations with MetS have been inconsistent [11,13,14]. These inconsistencies may reflect differences in MetS criteria employed to define MetS, population size, study design, gender, genetic heterogeneity or indeed the dietary environment of the populations studied. In the current study, we report increased MetS risk associated with rs7903146 T allele carriers, which may, at least in part, be accounted for by their impaired insulin sensitivity, greater insulin resistance, elevated insulin concentrations, increased

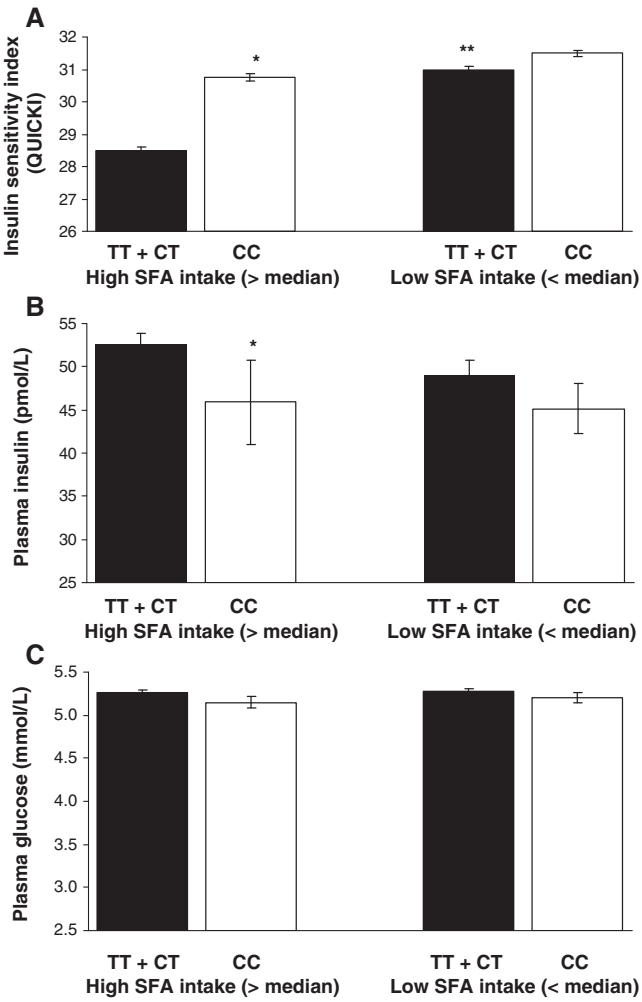

Fig. 1. Gene–nutrient interactions between *TCF7L2* rs7903146 and SFA intake on insulin sensitivity (A), plasma insulin (B) and glucose (C) concentrations. Values are means ±S.E.M. The black bars represent the T allele carriers (n=964), and the white bars represent the CC homozygotes (n=790). P values were calculated by GEE linear regression adjusting for potential confounding factors including age, gender, BMI, smoking status, energy intake, physical activity and medication use. Global gene–nutrient interaction for insulin sensitivity (P=.04) and insulin (P=.045). *P<.05, **P<.01; different from T allele carriers with high SFA intake.

abdominal obesity and hypertension. We also report gender differences wherein the deleterious effects of the rs7903146 T allele were only observed in the female participants. In addition, when genders were analyzed separately, differences observed between genotypes on metabolic variables in the whole population were mirrored only in the female subset. In keeping with these findings, Laramie et al. also showed a modest association between rs7903146 with T2DM risk, which when stratified by gender was only observed in women [36].

Genetic and environmental factors contribute to susceptibility to diet-related polygenic disorders such as obesity and MetS [16,17]. The first indication that environmental or lifestyle factors might influence the genetic effect of *TCF7L2* polymorphisms came from the Diabetes Prevention Program and the Diabetes Prevention Study [2,9]. In the Diabetes Prevention Study, overweight individuals with impaired glucose tolerance were allocated to an intensive diet and lifestyle intervention group or a control group. After a mean 4-year follow-up period, they found that *TCF7L2* polymorphisms were associated with the incidence of diabetes in the control group, but not the intervention group, suggesting that environmental factors can reduce genetic susceptibility even when risk genotypes are related to impaired insulin secretion [9].

Dietary fatty acids are key environmental factors in the pathogenesis and progression of MetS [15,16,20]. We report modulation of the genetic association between *TCF7L2* polymorphisms and MetS by dietary fat intake. In particular, high habitual dietary intake of SFA was associated with further deterioration in insulin sensitivity and increased MetS risk by approximately 52% in the minor T allele carriers compared to the major allele homozygotes. Interestingly, genetic susceptibility to impaired insulin sensitivity as well as MetS was not present among risk allele carriers with low SFA intake. Dietary fatty acids were calculated as percentage intake of total energy; thus, the amount of each fatty acid is relative to the remaining fatty acids. This approach makes direct inference regarding fatty-acid-specific effects difficult. However, our interaction and heterogeneity analysis confirmed the modulation of MetS risk by SFA, suggesting that SFA may be the most important fatty acid determinant of MetS risk. Saturated fat has a detrimental effect on insulin sensitivity, promoting the development of obesity and diabetes [20–22,37]. Our data suggest that *TCF7L2* rs7903146 risk genotypes are sensitive to dietary SFA and that these individuals may derive the most benefit from dietary manipulation and current guidelines to reduce dietary SFA intake. As SNPs are established at conception and diet was determined at baseline in this study, this begs the question of which variable is the "cause" and which is the "modulating factor." This is a common question in studies investigating gene–diet interactions. As diet is a modifiable factor, potential modulation of genetic effects by dietary factors may have important public health implications. Furthermore, pharmacogenetic studies have shown that *TCF7L2* variants influence therapeutic response to sulphonylureas in T2DM, wherein risk allele carriers of rs7903146 and rs12255372 had almost twofold greater likelihood of treatment failure with respect to achieving target HbA_{1c} concentrations [38,39]. Therefore, the potential of dietary therapies to attenuate this situation remains an intriguing possibility.

It is proposed that *TCF7L2* polymorphisms increase T2DM risk through altered *TCF7L2* gene expression, disturbed glucose homeostasis, impaired insulin secretion, attenuated insulin sensitivity and resultant insulin resistance [2,4,40,41]. In the current study, the risk allele carriers had higher fasting insulin concentrations and displayed impaired insulin sensitivity and greater insulin resistance compared to the CC homozygotes, thus contributing to their increased MetS risk. In keeping with previous findings [13,14], no differences were observed with respect to fasting glucose concentrations. In relation to potential functional effects of the *TCF7L2* rs7903146 polymorphism, the intronic location of this SNP has the potential to affect messenger RNA stability or modulate *TCF7L2* gene transcriptional activity. FASTSNP, a functional analysis tool [42], was used to predict how rs7903146 might impact on gene expression. The T allele, but not the C allele, of rs7903146 was identified as lying in a predicted intronic enhancer sequence homologous to a binding site for the transcription factors CDXA and E4BP4. The significance of this is unknown, but it is tempting to speculate that, in conditions such as MetS where insulin sensitivity/resistance is disturbed, further potential disruption to the Wnt signaling pathway arising from *TCF7L2* polymorphisms may interfere with normal insulin secretion and glucose homeostasis, thereby promoting an impaired insulin-sensitive or insulin-resistant phenotype. The mechanism whereby fatty acids can modulate the genetic risk conferred by *TCF7L2* polymorphisms as observed herein is unknown, and functional studies are required to ascertain the biological significance of such gene–diet interactions.

Several features of this study (prospective nature, comprehensive phenotypic characterization, large number of male and female cases and matched controls from all socioeconomic categories and

areas in the country) make this study particularly robust. Nevertheless, some limitations can be identified. As dietary consumption was self-reported by food-frequency questionnaire, some misclassification of exposure, due to deficiencies in nutrient databases, accuracy of memories or willingness to divulge these details, was inevitable. The number of dietary records used was minimal (three in a small number of subjects) but was necessitated in order to maximise the number of matched cases and controls. The focus of the current analysis was on dietary fat composition, but other food components such as carbohydrate or fiber can play a role in the development of the MetS. Finally, given the observational nature of the study, it is not possible to tell whether the associations which were identified in women, but not men, are of a causal nature or not.

In conclusion, this case–control study replicates the association between the *TCF7L2* rs7903146 polymorphism and MetS risk previously identified in population-based studies [11,12]. Furthermore, we report that dietary fat intake, in particular SFA, in the years prior to MetS case/control selection seemed to modulate the genetic susceptibility to impaired insulin sensitivity and MetS. Interestingly, the genetic associations and gene–diet interactions derived from the female subjects. Replication of these gene–diet interactions in an independent cohort should be valuable in validating these new findings. A better understanding of the molecular mechanisms underlying such gene–diet interactions may have implications in terms of developing personalized dietary treatment strategies.

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