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Variants of the Transcription Factor 7-Like 2 Gene (*TCF7L2*) are Strongly Associated with Type 2 Diabetes but not with the Metabolic Syndrome in the MONICA/KORA Surveys

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Key words
- type 2 diabetes
- TCF7L2
- association study
- SNP
- replication

Abstract

Recently, significant associations between common variants of the transcription factor 7-like 2 gene (*TCF7L2*) and type 2 diabetes have been reported. This study was designed to replicate the reported associations of the two highly correlated ($r^2 = 0.86$) *TCF7L2* single nucleotide polymorphisms rs12255372 and rs7903146 with type 2 diabetes in a case-control study of 2369 MONICA/KORA participants (678 cases/1691 controls from Augsburg, Germany). To further investigate the pathogenic mechanism underlying these associations, we extended our analyses to the metabolic syndrome (IDF, NCEP definitions) and its components in a population-based study comprising 1404 male and female KORA participants aged 55–74 years. Results of our analyses strongly confirmed the minor T alleles as risk variants for type 2 diabetes (rs7903146: OR_{TvsC} [95% CI] = 1.36 [1.18;1.58], p = 0.00003, and rs12255372: OR_{TvsG} [95% CI] = 1.31 [1.13;1.51], p = 0.0003). Moreover, the T allele at rs7903146 was inversely associated with log-transformed, HOMA-%B ($\beta = -0.07$, p = 0.005) as a measure of basal insulin secretion, and log-transformed fasting insulin ($\beta = -0.06$, p = 0.02). No association was found with insulin resistance (HOMA-IR) and the metabolic syndrome. These findings support replication evidence that *TCF7L2* variants increase type 2 diabetes risk. *TCF7L2* may primarily affect pancreatic beta cell function.

Introduction

Type 2 diabetes mellitus (T2DM) results from a complex interplay of environmental and genetic factors [1]. The identification of genes that predispose to T2DM could provide definite clues to understand its primary pathogenesis [2] and thus lead to improved prevention, diagnosis and treatment of the disease.

Recently, a strong association between T2DM and the microsatellite marker DG10S478 within intron 3 of the transcription factor 7-like 2 gene (*TCF7L2*) on chromosome 10q25.2 has been found in three independent case-control samples ($p = 2.1 \times 10^{-9}$) [3]. Similarly strong associations were reported for two of the gene's noncoding single nucleotide polymorphisms (SNPs), rsl2255372 and rs7903146, which were highly correlated with DG10S478 ($r^2 = 0.95$ and $r^2 = 0.78$, respectively) [3]. Another study found these polymorphisms to predict the progression to diabetes in high-risk, overweight persons and to be associated with impaired β-cell function [4].

Validation of association results of specific genetic variants underlying complex polygenic diseases has proven essential as many initially reported disease associations were not replicated by later studies [5]. Furthermore, probably due to bias and genuine population diversity, almost all initial findings of susceptible genetic polymorphism overestimated the true effects [6]. Finally, although *TCF7L2* is widely expressed and known to respond to developmental signals from members of the Wnt family of proteins [7,8], the pathophysiological mechanism of *TCF7L2* variants, that influence metabolic disorders, remains unclear [9].

The present study was designed to replicate the reported association of the two *TCF7L2* polymorphisms rs12255372 and rs7903146 with T2DM in 2369 participants of the population-based MONICA/KORA surveys (Augsburg, Southern Germany). To further investigate the pathogenic mechanism of *TCF7L2* variants and T2DM, we extended our analyses to the metabolic syndrome and its components.

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Research Design and Methods

Study populations and outcome definitions

This study is based on data from 2369 participants of four independent cross-sectional surveys (S1–S4) carried out within the WHO MONICA (MONItoring Trends and Determinants in CArdiovascular disease; S1–S3) and the KORA (Cooperative Health Research in the Region of Augsburg; S4) project between 1984 and 2001 [10–12]. All four surveys were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the ethics committee of the Bavarian Medical Association. Written informed consent was obtained from all subjects.

For the analysis of the association of *TCF7L2* and T2DM, we used a case-control design including 558 previously known and 120 newly detected T2DM cases from all four surveys and 1691 non-diabetic controls from survey S4 (2369 subjects in total). Previously known T2DM was defined based on self-reported physician diagnosis, which was confirmed by the patients' general practitioners, or use of antidiabetic agents. Newly detected T2DM was diagnosed by means of an oral glucose tolerance test (OGTT), that was performed in all 55–74 year-old, initially non-diabetic S4 participants as previously described [2].

The association between *TCF7L2* and the metabolic syndrome as well as its components was tested with a population-based study design including all fasting 55–74 year-old S4 participants (1404 subjects). All except for 19 S4 participants with previously known T2DM were non-fasting and thus excluded. The metabolic syndrome was defined, 1) according to the International Diabetes Federation (IDF) criteria for European populations [13, 14], and 2) according to the National Cholesterol Education Program (NCEP) criteria [15, 16]. Anthropometric and laboratory measurements of all quantitative measures used in the analyses were carried out as described previously [2]. Subjects taking medication that substantially influences the analyzed outcome, were excluded from analysis of this outcome as described in the table footnotes. Basal insulin secretion was assessed by HOMA-%B, which was calculated as (fasting plasma insulin [mU/l]×20)/(fasting plasma glucose [mmol/l] – 3.5). Insulin sensitivity was evaluated using HOMA-IR, and calculated as (fasting plasma insulin [mU/l])×(fasting plasma glucose [mmol/l])/22.5) [17].

Genotyping

Genotyping of the *TCF7L2* variants was carried out with matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectroscopic analysis of allele-dependent primer extension products as described previously [18]. The genotyping success rates were 98.3 % for rs12255372, and 97.3 % for rs7903146.

Statistical Analyses

Each SNP was tested for deviation from Hardy–Weinberg equilibrium by means of Fisher's exact test in controls of the case-control sample and in all subjects of the population-based sample. Associations between genotypes and T2DM or the metabolic syndrome were assessed by multiple logistic regression. Quantitative traits were analyzed by multiple linear regression. Traits that were not normally distributed were log-transformed to reach normality, or analyzed by the non-parametric Kruskal–Wallis test if this was not successful (HOMA-IR). All analyses were adjusted for age and sex, as well as body mass index (BMI) if indicated, and tested for interactions between genotypes and these covariates. As no major population stratification was detected within the KORA population [19], it was not necessary to control for effects of admixture. Due to the high correlation between the two analyzed SNPs and because the analyses represent confirmative testing of reported associations, it was also not necessary to adjust the significance level for multiple testing for the main analyses within the case-control study; p values <0.05 were considered statistically significant here. In contrast, all analyses conducted within the population-based sample are explorative in nature and results with p values <0.05 are discussed with all due caution and have to be confirmed by future studies. As Grant et al. detected the best fit for the multiplicative genotype model [3], we computed multiplicative genotype models as well as model-free estimates for both SNPs. All analyses were performed with SAS software (V 9.1., Cary, NC, USA), all presented p values are two-sided.

Results

Characteristics of study participants

Two study populations were analyzed: one case-control sample including 2369 participants, and one population-based sample of 1404 participants. Characteristics and *TCF7L2* genotype frequencies of study participants are shown in **Tab. 1** for the case-control sample and **Tab. 2** for the population-based sample. No deviations of genotype distributions from Hardy–Weinberg equilibrium were found in either sample, with all p values being larger than 0.05. The frequencies of the minor T alleles within the population-based sample were 0.27 for rs12255372 and 0.28 for rs7903146 and thus similar to those previously reported [3]. Within the case-control sample, the frequencies of the minor T alleles were 0.33 for rs12255372 and 0.34 for rs7903146 in T2DM cases, whereas allele frequencies in controls were similar to those of the population-based sample. Linkage disequilibrium between both variants was strong ($D' = 0.88$, $r^2 = 0.86$).

Association of *TCF7L2* variants and T2DM

The multiple analyses in the sample of 678 cases and 1691 controls identified the T alleles at both SNPs as risk variants for T2DM, with significant associations for model-free estimates and the multiplicative genotype model (**Tab. 3**). The results dem-

Tab. 1 Characteristics and *TCF7L2* genotype frequencies of participants in the case-control sample (n = 2369), stratified by type 2 diabetes case/control status

	Cases	Controls
n total (male/female)	678 (393/285)	1691 (870/821)
Age [years]	62.5 ± 7.8	60.8 ± 8.7
Body mass index [kg/m^2]	30.3 ± 4.6	28.1 ± 4.3
rs7903146 CC n (%)	282 (43.3)	842 (51.3)
CT n (%)	296 (45.5)	678 (41.3)
TT n (%)	73 (11.2)	121 (7.4)
rs12255372 GG n (%)	306 (45.9)	853 (51.4)
GT n (%)	287 (43.0)	698 (42.1)
TT n (%)	74 (11.1)	107 (6.5)

Data are presented as means ± standard deviations for age and body mass index, and as absolute numbers and frequencies for genotypes.

Tab. 2 Characteristics and *TCF7L2* genotype frequencies of participants in the population-based sample (n = 1404)

	n	Mean, median or frequency
Male [%]	1404	51.8
Age [years]	1404	64.0 ± 5.5
Body mass index [kg/m^2]	1398	28.4 ± 4.2
Weight [kg]	1399	77.9 ± 13.1
Height [cm]	1402	165.6 ± 8.9
Hip circumference [cm]	1403	106.2 ± 8.7
Waist circumference [cm]	1403	95.7 ± 11.6
Serum uric acid [mg/dl]	1403	5.66 ± 1.42
HbA1c [%]	1400	5.66 ± 0.50
Total cholesterol [mmol/l][1]	1239	6.31 ± 1.07
HDL cholesterol [mmol/l][1]	1238	1.51 ± 0.43
LDL cholesterol [mmol/l][1]	1237	4.01 ± 1.01
Triglycerides [mg/dl][1]	1229	113 (83;156)
Fasting plasma glucose [mg/dl][2]	1382	99 (93;108)
2-h plasma glucose [mg/dl][2]	1344	115 (94;143)
Fasting insulin [mU/l][2]	1333	10.1 (7.1;14.6)
HOMA-%B [(mU/l)/(mmol/l)][2]	1333	99.6 (71.2;138.8)
HOMA-IR [(mU/l)×(mmol/l)][2]	1327	2.49 (1.67;3.77)
Diastolic blood pressure [mmHg][3]	908	79.5 ± 9.8
Systolic blood pressure [mmHg][3]	908	133.5 ± 19.6
rs7903146 CC [%]	707	51.31
CT [%]	569	41.29
TT [%]	102	7.40
rs12255372 GG [%]	723	52.24
GT [%]	571	41.26
TT [%]	90	6.50

Data are presented as means ± standard deviation, medians (25th; 75th percentiles) for traits that are not normally distributed, or relative frequencies for sex and genotypes. [1] 163 subjects with lipid-lowering treatment were excluded. [2] 19 subjects with previously diagnosed type 2 diabetes were excluded. [3] 490 subjects with antihypertensive treatment were excluded.

onstrated a copy-number effect and provided good fit for the multiplicative genotype model, the odds ratio (OR) with 95% confidence interval [95% CI] for T2DM being higher for homozygous than for heterozygous T allele carriers at rs7903146 (model-free estimates: OR_{TTvsCC} [95% CI] = 1.92 [1.38;2.67], p = 0.0001; OR_{CTvsCC} [95% CI] = 1.33 [1.09;1.62], p = 0.006; multiplicative model: OR_{TvsC} [95% CI] = 1.36 [1.18;1.58], p = 0.00003). Similar results were observed for rs12255372 (model-free estimates: OR_{TTvsGG} = 2.00 [1.43;2.80], p = 0.00005; OR_{GTvsGG} = 1.16 [0.95;1.41], p = 0.14; multiplicative model: OR_{TvsG} = 1.31 [1.13;1.51], p = 0.0003). Analyses were adjusted for sex, age and BMI. No major differences between adjusted and unadjusted results as well as no associations for interactions between these covariates and the analyzed genotypes were detected (data not shown).

Association of *TCF7L2* variants and the metabolic syndrome or related traits

Analyses regarding the association of *TCF7L2* variants and the metabolic syndrome were performed within the population-based sample. In this elderly population, 52% (n = 730) met the IDF criteria, and 27% (n = 370) met the NCEP criteria for the metabolic syndrome. Compared with the remaining 662 (IDF) or 1024 (NCEP) subjects, neither of the two SNPs was statistically significantly associated with the metabolic syndrome according to the multiplicative genotype model (**Tab. 4**) or model-free estimates (data not shown). We further examined whether the risk alleles of either SNP affected quantitative parameters related to the metabolic syndrome. The results of the analyses using multiplicative genotype models are shown in **Tab. 4**. The T allele at rs7903146 was inversely associated with log-transformed HOMA-%B ($\beta = -0.07$, p = 0.005) as a measure of basal insulin secretion, and log-transformed fasting insulin ($\beta = -0.06$, p = 0.02).

Discussion

Replication studies of initially reported associations between genetic variants and complex diseases with polygenic etiology have often revealed false-positive findings in the past. Only a few genetic variants have been identified as susceptibility genes for T2DM so far [5], altering the T2DM risk by approximately 15 to 20% [20]. However, risk modifications of newly identified genetic variants in the *TCF7L2* gene seem to be substantially greater [3,4]. As most early association studies overestimate

Tab. 3 Association of *TCF7L2* variants with type 2 diabetes in the case-control sample

SNP	n cases/controls	Genotype model	OR [95%CI][1]	p
rs7903146	647/1632	Model-free CT vs. CC	1.33 [1.09;1.62]	0.006
		TT vs. CC	1.92 [1.38;2.67]	0.0001
		Multiplicative T vs. C	1.36 [1.18;1.58]	0.00003
rs12255372	663/1649	Model-free GT vs. GG	1.16 [0.95;1.41]	0.14
		TT vs. GG	2.00 [1.43;2.80]	0.00005
		Multiplicative T vs. G	1.31 [1.13;1.51]	0.0003

[1] Adjusted for age, sex and body mass index (stratified into < 18.5; ≥ 18.5 to < 25 (reference); ≥ 25 to < 30; ≥ 30 to < 35; ≥ 35 to < 40; ≥ 40 kg/m^2).

Tab. 4 Association of *TCF7L2* variants with the metabolic syndrome or related quantitative traits in the population-based sample, multiplicative genotype model

	rs7903146			rs12255372		
Logistic regression	**n**	**OR [95 %CI]**	**p**	**n**	**OR [95 %CI]**	**p**
Metabolic syndrome – IDF	1367	1.05 [0.88;1.25]	0.58	1373	1.08 [0.90;1.28]	0.41
Metabolic syndrome – NCEP	1370	0.96 [0.79;1.16]	0.68	1376	1.01 [0.83;1.23]	0.89
Linear regression	**n**	**β**	**p**	**n**	**β**	**p**
Body mass index [kg/m^2]	1372	−0.106	0.56	1378	0.120	0.51
Weight [kg]	1373	−0.356	0.48	1379	0.263	0.61
Height [cm]	1376	−0.087	0.73	1382	−0.045	0.86
Hip circumference [cm]	1377	−0.362	0.32	1383	0.158	0.67
Waist circumference [cm]	1377	−0.502	0.25	1383	−0.017	0.97
Waist-hip-ratio	1377	−0.002	0.50	1379	−0.001	0.62
Serum uric acid [mg/dl]	1372	0.026	0.61	1378	0.009	0.87
HbA1c [%]	1371	−0.002	0.94	1377	−0.014	0.52
Total cholesterol [mmol/l][1]	1211	0.036	0.46	1216	0.022	0.65
HDL cholesterol [mmol/l][1]	1210	−0.009	0.61	1215	−0.022	0.21
LDL cholesterol [mmol/l][1]	1209	0.043	0.35	1214	0.038	0.42
Triglycerides [mg/dl][1,2]	1202	0.004	0.84	1207	0.016	0.44
Fasting plasma glucose [mg/dl] [2,3]	1352	0.005	0.37	1358	0.002	0.74
2-h plasma glucose [mg/dl][2,3]	1316	−0.003	0.85	1322	−0.003	0.84
Fasting insulin [mU/l][2,3]	1309	−0.058	0.02	1314	−0.042	0.10
HOMA-%B [(mU/l) / (mmol/l)][2,3]	1309	−0.073	0.005	1314	−0.047	0.07
Diastolic blood pressure [mmHg][4]	884	−0.449	0.65	886	−0.742	0.46
Systolic blood pressure [mmHg][4]	884	−0.618	0.22	886	−0.565	0.27
Kruskal–Wallis test	**n**	**Median (25th; 75th percentiles)**	**p**	**n**	**Median (25th; 75th percentiles)**	**p**
HOMA-IR [(mU/l) × (mmol/l)][3,5]						
AA	678	2.55 (1.68;4.00)	0.13	691	2.54 (1.69;3.96)	0.31
Aa	539	2.39 (1.67;3.63)		541	2.42 (1.63;3.62)	
aa	92	2.35 (1.49;3.50)		82	2.51 (1.58;3.77)	

All parametric analyses were adjusted for age, sex and body mass index (stratified into <18.5; ≥18.5 to <25 (reference); ≥25 to <30; ≥30 to <35; ≥35 to <40; ≥40 kg/m^2), except analyses of metabolic syndrome, body mass index, weight, height, hip and waist circumference, and waist-hip-ratio, for which adjustment was limited to age and sex. [1]Subjects with lipid-lowering treatment were excluded. [2]Log-transformed traits. [3]Subjects with previously diagnosed type 2 diabetes were excluded. [4]Subjects with antihypertensive treatment were excluded. [5]rs12255372: AA = GG, Aa = GT, aa = TT; rs7903146: AA = CC, Aa = CT, aa = TT.

genetic effects [6], validation not only of reported genetic associations, but also of their effect sizes is essential.

In our large, population-based KORA samples with well-phenotyped participants reflecting the Southern German population [10], we could replicate the reported associations of the *TCF7L2* SNPs rs12255372 and rs7903146 with T2DM. Our replication results strongly confirmed the T alleles at both SNPs as risk variants for T2DM. Compared to previously reported allele frequencies [3], the T allele frequencies were slightly lower in diabetic cases, but almost identical in controls, resulting in slightly smaller association estimates. Furthermore, our results strongly confirmed initial findings of good fit for the multiplicative genotype models, as a clear copy-number effect was found, especially for SNP rs7903146. While this manuscript was in preparation, eight other studies conducted independently from ours at the same time found similar results on *TCF7L2* gene variants and type 2 diabetes [21–28]. Taken together, these data provide strong evidence that *TCF7L2* is a true diabetes susceptibility gene (**Tab. 5**).

We extended our analyses to the metabolic syndrome and related components, because individuals with the syndrome are at significantly increased risk of type 2 diabetes mellitus [29] and because the pathophysiological mechanism of *TCF7L2* variants is still unclear. The analyzed quantitative traits included body mass index, fasting insulin, HOMA-IR and HOMA-%B, which are highly relevant for the development of T2DM. Although we analyzed an elderly population with a high prevalence of the metabolic syndrome, neither of the two SNPs was statistically significantly associated with the metabolic syndrome. This lack of an association could be due to several rea-

Tab. 5 Recent studies on TCF7L2 variants rs7903146 and rs12255372 in combined or single analysis

Reference	Study information	Ethnicity	n Patients	n Controls	Variation	Odds Ratio CT vs. CC	Odds Ratio TT vs. CC	Odds Ratio Additive model	P[1]
Grant [3]	CC	Caucasians (Iceland, Denmark, USA)	1185/228/361	931/539/530	rs7903146			1.49 [1.35;1.65]	3.9×10–15
					rs12255372			1.52 [1.38;1.68]	2.5×10–16
					combined	1.45 [1.26;1.67]	2.41 [1.94;3.00]	1.56 [1.41;1.73]	4.7×10^{-18}
Humphries [24]	NPHSII	Caucasians	158	2518	combined	1.65 [1.13;2.41]	1.87 [0.99;3.53]		<0.01
		(Europe)	1459	2518	combined	1.43 [1.24;1.65]	2.11 [1.69;2.63]		<0.0001
		Asians (India)	919	919	combined	1.50 [1.14;1.99]	1.64 [1.03;2.63]		0.003
		Afro-Caribbean	385	385	combined	1.25 [0.90;1.75]	1.32 [0.74;2.33]		0.17
van Vliet-Ostaptchouk [27]	CC	Caucasians (Netherlands)	502	920	combined		1.38		
Cauchi [21]	CC	Caucasians (France)	2367	2499	rs7903146		1.69 [1.55;1.83]		6.0×10^{-35}
					rs12255372		1.60 [1.47;1.74]		7.6×10^{-28}
Saxena [25]	CC	Caucasians (Scandinavia, Sweden, Poland, US, Botnia, Finnland)	3563	3563	rs7903146	1.40 [1.27;1.55]	1.86 [1.55;2.23]	1.39 [1.29;1.50]	1.55×10^{-17}
	Different family samples	Caucasians (Scandinavia, Finnland, Botnia)	569	615	rs7903146			1.48 [1.17;1.87]	4.69×10^{-4}
Damcott [22]	CC	Caucasians (Amish)	137 (+139IGT)	342	rs7903146		1.57		0.008
					rs12255372		1.4		0.04
Scott [26]	CC	Caucasians (Finnland)	1151	953	rs7903146			1.33 [1.14;1.56]	0.00042
					rs12255372			1.36 [1.15;1.61]	0.00026
Zhang [28]	Nurses health study (CC) only women	Caucasians (USA)	687	1051	rs12255372	1.25 [1.01;1.55]	1.86 [1.30;2.67]	1.32 [1.13;1.54]	0.0002
	Health professional Follow-up Study (CC) only men		886	896	rs12255372	1.63 [1.32;2.02]	2.15 [1.48;3.13]	1.53 [1.31;1.80]	<0.0001
	Nested CC		1573	1947	rs12255372	1.43 [1.23;1.66]	1.99 [1.54;2.59]	1.42 [1.27;1.59]	<0.0001
	Meta analysis		3347	3947	rs12255372			1.48 [1.37;1.60]	1×10^{-16}
Groves [23]	Parent offspring trios (388)	Caucasians (UK)	2158	2574	rs7903146	1.35 [1.19;1.53]	1.90 [1.54;2.33]	1.36 [1.24;1.48]	1.3×10^{-11}
					rs12255372	1.30 [1.15;1.47]	1.66 [1.35;2.05]	1.29 [1.18;1.41]	2.2×10^{-8}

[1]p values for additive models or combined analysis; CC

sons. First, not all subjects with the metabolic syndrome will eventually develop type 2 diabetes. In the Insulin Resistance Atherosclerosis Study (IRAS), a prospective multi-ethnic epidemiologic study in the U.S., the population attributable-risk percent of incident diabetes was 49% for the IDF and 46% for the NCEP syndrome definition, respectively [29]. Thus, less than 50% of the risk of type 2 diabetes was attributable to the presence of the metabolic syndrome. A possible explanation for this finding might lie in the substantial heterogeneity of the metabolic syndrome allowing for many combinations of metabolic disturbances with different implications for diabetes risk, but resulting in the same diagnosis. Second, it is possible that there are distinct polygenic determinants of the metabolic syndrome with small effect sizes, which could not be observed in our study and would require an even larger sample. Thus, it is conceivable that we could find a significant association of *TCF7L2* variants with type 2 diabetes, but not with the metabolic syndrome.

When investigating single or related parameters of the metabolic syndrome, the strongest association was found for decreased basal insulin secretion, assessed by HOMA-%B, and the T2DM risk-conferring T allele at rs7903146. This finding is plausible and in line with a previous report based on the T2DM high-risk population of the Diabetes Prevention Program (DPP), demonstrating that persons who are homozygous for the risk allele at rs7903146 have lower first phase insulin secretion in response to an OGTT than homozygous non-carriers of the risk allele [4]. On the other hand, insulin sensitivity was significantly higher in the DPP, which correlated with lower mean BMI and waist circumference. As discussed by the authors, the unexpected finding of higher insulin sensitivity in carriers of the T allele could result from the selected DPP study population, which included overweight persons with impaired glucose tolerance. A study in an Amish population gives further conflicting results [22]. In nondiabetic Amish subjects (n = 698), no association of OGTT-derived insulin resistance (HOMA-IR) and insulin secretion measurements with the TCF7L2 gene variants was observed [22]. In addition, intravenous glucose tolerance tests were carried out in a small sample of 48 nondiabetic non-Amish subjects, which indicated that rs7901695 and rs79003146 were significantly associated with both a reduction in insulin sensitivity and a defect in insulin secretion [22]. The present study provides novel evidence from a population-based study. In the KORA S4 survey we confirm the results from the large Amish population that there is no association between *TCF7L2* polymorphisms and insulin sensitivity, assessed by HOMA-IR. Our data suggest that the higher risk of diabetes in carriers of the T allele is primarily conferred by an impaired insulin secretion.

The *TCF7L2* gene product is a high-mobility-group box containing transcription factor that suppresses rather than activates gene expression [7, 8, 30]. It has been suggested, that the association with T2DM may result from impaired regulation of gene expression of the insulinotropic proglucagon in enteroendocrine cells via the Wnt signalling pathway [3, 31], but the precise mechanisms underlying the reduced insulin secretion require further investigation.

Taken together, we found a significant association of *TCF7L2* gene variants and type 2 diabetes in a large sample from the Southern German KORA study, thus confirming previous findings. In addition, we did not detect a significant association of these SNPs with insulin resistance (HOMA-IR), the metabolic syndrome or any of its components. There was a significant trend towards lower levels of fasting insulin and reduced basal insulin secretion (HOMA-%B) in the individuals who were homozygous for the type 2 diabetes risk allele of rs7903146. This finding supports the hypothesis that *TCF7L2* variants may primarily affect pancreatic beta cell function, leading to impaired insulin secretion and eventually to type 2 diabetes.

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