P-0632 The association of TCF7L2, KCNJ11, CDKAL1 gene, and FTO genes with T2DM in Emirati population

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BACKGROUND

T2DM is a multifactorial disease caused by a complex interplay of MULTIPLE GENETIC VARIANTS and many environmental factors. Many gene variants were confirmed and linked to the pathogenesis of T2DM by influencing either insulin secretion, insulin sensitivity, glucose metabolism, or all of them ¹. Genetic variations such as rs7903146 (TCF7L2), rs5219 (KCNJ11), rs10946398 (CDKAL1), and rs9939609 (FTO) are known to be linked to T2DM in many ethnic groups. The worldwide prevalence of the disease is predicted to reach 642 MILLION cases by 2040 ². 21% of Emirati adults were reported to be suffering from Diabetes ³.

OBJECTIVE OF THE STUDY

To investigate the possible association of the Single Nucleotide Polymorphisms (SNPs) rs7903146 (TCF7L2), rs5219 (KCNJ11), rs10946398 (CDKAL1), and rs9939609 (FTO) with the susceptibility of T2DM among Emirati population

METHODS

- ✓ The study included 264 (134 males, 130 females) unrelated diabetic patients and 153 unrelated healthy controls (44 males, 109 females) from Emirati population.
- ✓ DNA was extracted from participants' saliva samples and genotyped for the four SNPs using TaqMan® real-Time PCR assays.
- ✓ STATA13 and R software were used for the statistical analysis.

REFERENCES

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RESULTS

ANALYSIS 1: The collected demographic data and biochemical characteristics of the 417 volunteers were analyzed using t-test for continuous phenotypes and for proportions using Chi-square test.

FINDINGS: The diabetic patients significantly showed higher mean age, higher BMI values ($p<0.0001$), systolic blood pressure values ($p<0.0001$), and glycosylated hemoglobin (HbA1c) ($p<0.0001$) than controls.

ANALYSIS 2: Multiple logistic regression model was adopted incorporating age, gender, and BMI as covariates; in order to test the associations between the SNPs and T2DM.

FINDINGS: These covariates were significantly different between T2DM and their healthy controls (**Table 1**).

Table 1: Associations of the SNPs with type 2 diabetes mellitus in Emirati population

SNP	A1/A2*	MAF (%)		OR (95% CI) **	P-value†	
		Case	Control		Unadj.	Adj.
rs7903146	T/C	42.23	37.25	1.80 (1.18-2.69)	0.146	0.0063
rs5219	T/C	26.52	29.41	0.82 (0.53-1.25)	0.354	0.325
rs10946398	C/A	29.36	24.84	1.13 (0.76-1.69)	0.209	0.551
rs9939609	T/A	39.87	42.61	1.14 (0.79-1.64)	0.461	0.484

* A1/A2: minor to major alleles.
** Odds ratios and 95% confidence intervals for the adjusted P-values, calculated based on the minor allele as a reference.
† P-value before and after adjustment for age, gender, and body mass index. Significant P-values are shown in bold. Abbreviations: CI: confidence intervals; MAF: minor allele frequency; OR: odds ratio.

ANALYSIS 3: Interaction between the SNP rs7903146 in TCF7L2, and clinical variables was tested using a logistic regression model that adopted the interaction term (*) in R statistical software.

FINDINGS: The genetic effect of the locus in T2DM susceptibility was stronger in older population compared with the younger age group. Adding obesity for this interaction has indicated a slightly stronger association ($p=0.026$), indicating these factors are risk factors for the development of the disease (especially age and the rs7903146) (**Table 2**).

Table 2: Interaction effects of the SNP rs7903146 in TCF7L2, Age, Gender, and BMI on the susceptibility of T2DM

	SNP: Gender	SNP: Age	Gender :Age	SNP :BMI	Gender :BMI	Age: BMI	SNP:G ender: Age	SNP: Gender: BMI	SNP: Age: BMI	Gender :Age: BMI	SNP: Gender: Age: BMI
Estimate (Beta)	-1.349	-0.038	-0.022	-0.059	-0.030	-0.001	0.035	0.038	0.001	0.001	-0.001
Standard error	1.232	0.017	0.029	0.033	0.052	0.001	0.021	0.039	0.001	0.001	0.001
P-value	0.274	0.029	0.447	0.075	0.559	0.123	0.103	0.331	0.026	0.346	0.118

*Beta: regression coefficient for interaction in logistic regression.
BMI: body mass index; TCF7L2: Transcription factor 7-like 2; T2DM, type 2 diabetes mellitus.

ANALYSIS 4: The association of TCF7L2, KCNJ11, CDKAL1, and FTO variants and the quantitative traits related to the susceptibility of T2DM were stratified. Individuals homozygous for protective alleles for each SNP were compared to those carried one or two copies of risk alleles assuming a dominant effect.

FINDINGS: For rs7903146 SNP; no significant differences in the demographic and anthropometric parameters between the CC genotype and the combined genotypes for the risk allele (CT+TT). For rs5219 SNP; only BMI ($p=0.032$) and diastolic blood pressure ($p=0.041$) showed significant difference between T2DM patients with the CC genotype versus combined CT+TT genotype. For rs10946398 SNP; no significant differences were observed with the AA genotype and those that carried the C allele in the combined genotype (AC+CC), except for HbA1c ($p=0.025$) and fasting blood glucose ($p=0.036$). For rs9939609 SNP, the differences were significant between T2DM patients with the AA genotype versus AT+TT genotype, for BMI ($p=0.014$), systolic blood pressure ($p=0.044$) and fasting blood glucose ($p=0.034$).

CONCLUSION

This study confirmed that TCF7L2 is a risk locus of T2DM in Arab descends form UAE, with the T allele of the SNP rs7903146 considered as the risk for the disease as widely reported. Although we did not find associations with the other known T2DM-related loci (KCNJ11, CDKAL1, and FTO), we observed that these loci influence some T2DM-related traits like BMI.