Replication of Genome Wide Association-Validated Loci for Type 2 Diabetes Mellitus in the Saudi Arabian Population

Nasser M. Al-Daghri 1, 2, 3, Khalid M Alkharfy 1,2,4, Majed S. Alokail 1, 2, 3, Amal M. Alenad5, Omar S. Al-Attas 1, 2, 3, Abdul Khader Mohammed1,3, Shaun Sabico 1,3, Omar M.E. Albagha6

1Biomarkers Research Program, Biochemistry Department, College of Science, King Saud University; 2Center of Excellence in Biotechnology Research Center, King Saud University; 3Prince Mutaib Chair for Biomarkers of Osteoporosis, King Saud University, 4Clinical Pharmacy Department, College of Pharmacy, King Saud University;5 School of Biological Sciences, Life Science Building 85, University of Southampton, Southampton SO17 1BJ, UK; 6 Rheumatic Diseases Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health problem worldwide and the prevalence of this disease in Saudi Arabia is among the highest in the world. Although lifestyle and environmental factors contribute to T2DM risk, genetic factors have been widely studied in many populations. Previous genome wide association studies in European and other populations have identified over 35 loci for T2DM risk. However, little is known about the contribution of these loci to T2DM in the Saudi Arabian population.

Methods

In this study we investigated for the first time, the association of 38 previously identified T2DM risk loci (32 loci from European and 6 loci from South Asian populations) in 1,166 T2DM patients and 1,235 healthy controls from Saudi Arabia.

Results

Common genetic variants (in or near WFS1, JAZF1, CDKN2A/B, TCF7L2, KCNQ1, HNF4A, and DUSP9) showed significant (P< 0.05) associations with T2DM in our study population. The effect sizes of these loci were comparable to those previously identified with the exception of HNF4A which showed a trend for larger effect size in our study population (OR, 95% CI; 1.27, 1.07–1.51) compared to that reported in South Asian populations (1.09, 1.06-1.12, I2 = 65.9). Analysis of risk allele scores (RAS) defined by the T2DM-associated loci showed that subjects in the top 20% of the RAS distribution (n = 480) had 2.5 fold increase in disease risk as compared to those in the bottom 20% (n = 480; P = 9.5 x 10-12). RAS were also associated with fasting glucose level (β = 0.12; P = 2.2 x 10-9) but not with BMI (P = 0.19).

Figure 1. Cumulative contribution of the 8 significant loci to the risk of T2D. A) Risk allele scores defined by the eight loci associated with T2D risk is plotted against the odds ratio (OR) for T2D. Risk alleles were weighted according to their estimated effect size and weighted risk allele scores were divided into five equal parts (quintiles; Q). The OR for T2D risk was calculated for each quintile in reference to the third Quintile (Q3). B) Risk allele scores in realtion to fasing glucose level. C) Risk allele scores in realtion to BMI. *P<0.05; Vertical bars represent 95% confidence intervals.

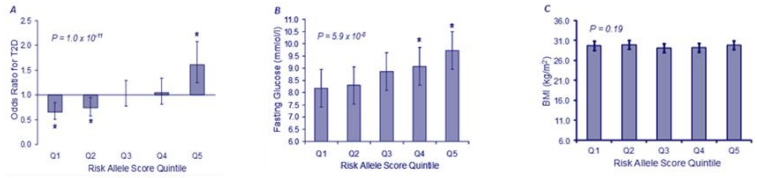

Figure S1. ROC curve analysis of loci associated with T2D in the Saudi population.

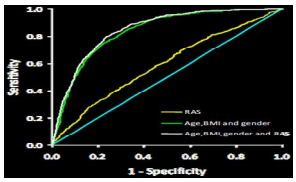

Table 1. Relevant characteristic of the study population

Characteristic	Control Group	T2D Group
Number	1235	1166
Males (%)	40.3	46.7
Females (%)	59.7	53.3
Age (years)	41.1 ± 11.7	55.8 ± 11.6
Weight (Kg)	74.2 ± 16.5	79.6 ± 16.0
Height (cm)	161.4 ± 9.1	159. ± 9.3
BMI (kg/m²)	28.4 ± 6.1	31.2 ± 6.2
Total cholesterol (mmol/l)	5.09 ± 1.02	5.42 ± 1.26
Triglycerides (mmol/l)	1.54 ± 0.93	2.25 ± 1.34
Fasting Glucose (mmol/l)	5.10 ± 0.65	11.6 ± 4.77

Table 2 Association of 37 SNPs with Type 2 diabetes in the Saudi population

Chr	SNP	Nearest Gene	Risk Allele	Saudi Population effect size		Previously reported effect size		Heterogeneity	
				OR (95%CI)	P value	Population*	OR (95% CI)	P	I²
1	rs10923931	NOTCH2	T	0.99 (0.80-1.24)	0.96	European	1.14 (1.07-1.21)	0.23	32.0
2	rs11899863	THADA	C	0.88 (0.62-1.24)	0.46	European	1.17 (1.09-1.25)	0.11	60.4
2	rs243021	BCL11A	A	0.99 (0.86-1.15)	0.94	European	1.09 (1.05-1.14)	0.20	38.7
2	rs3923113	GRB14	A	0.94 (0.81-1.09)	0.40	South Asian	1.09 (1.06-1.13)	0.05	73.5
2	rs7578326	IRS1	A	1.07 (0.93-1.24)	0.37	European	1.12 (1.07-1.17)	0.55	0.0
3	rs13081389	PPARG	A	0.89 (0.63-1.25)	0.50	European	1.24 (1.14-1.35)	0.07	70.1
3	rs6795735	ADAMTS9	C	0.96 (0.82-1.13)	0.62	European	1.09 (1.04-1.13)	0.14	53.8
3	rs16861329	ST6GAL1	G	1.10 (0.90-1.35)	0.36	South Asian	1.09 (1.06-1.12)	0.93	0.0
4	rs1801214	WFS1	T	1.26 (1.09-1.46)	1.63×10^{-3}	European	1.13 (1.08-1.18)	0.16	49.3
5	rs4457053	ZBED3	G	1.09 (0.94-1.26)	0.28	European	1.16 (1.10-1.23)	0.44	0.0
6	rs10440833	CDKAL1	A	1.05 (0.89-1.24)	0.54	European	1.25 (1.20-1.31)	0.04	75.9
7	rs849134	JAZF1	A	1.20 (1.04-1.39)	0.02	European	1.13 (1.08-1.17)	0.44	0.0
7	rs972283	KLF14	G	1.09 (0.94-1.26)	0.25	European	1.10 (1.06-1.15)	0.91	0.0
8	rs898854	TP53INP1	T	1.07 (0.93-1.23)	0.34	European	1.10 (1.06-1.15)	0.71	0.0
8	rs3802177	SLC30A8	G	1.22 (0.99-1.50)	0.06	European	1.15 (1.10-1.21)	0.58	0.0
9	rs10965250	CDKN2A/B	G	1.22 (1.03-1.44)	0.02	European	1.20 (1.13-1.27)	0.86	0.0
9	rs13292136	CHCD9	C	0.98 (0.55-1.75)	0.95	European	1.20 (1.11-1.29)	0.50	0.0
10	rs12779790	CDC123	G	1.06 (0.87-1.29)	0.55	European	1.09 (1.04-1.15)	0.78	0.0
10	rs1802295	VPS26A	A	0.94 (0.81-1.10)	0.46	South Asian	1.08 (1.05-1.12)	0.08	67.5
10	rs5015480	HHEX	C	1.07 (0.91-1.26)	0.40	European	1.18 (1.13-1.23)	0.24	26.7
10	rs7903146	TCF7L2	T	1.55 (1.33-1.80)	1.13×10^{-8}	European	1.40 (1.34-1.46)	0.20	38.2
11	rs231362	KCNQ1	G	1.17 (1.02-1.35)	0.03	European	1.11 (1.06-1.16)	0.48	0.0
11	rs163184	KCNQ1	G	1.16 (1.01-1.33)	0.04	European	1.09 (1.04-1.13)	0.42	0.0
11	rs5215	KCNJ11	C	1.11 (0.92-1.33)	0.29	European	1.09 (1.05-1.14)	0.85	0.0
11	rs1552224	CENTD2	A	0.97 (0.63-1.50)	0.88	European	1.13 (1.07-1.19)	0.50	0.0
11	rs1387153	MTNR1B	T	0.98 (0.84-1.15)	0.81	European	1.12 (1.07-1.17)	0.12	59.6
12	rs1531343	HMGA2	C	0.99 (0.84-1.16)	0.87	European	1.20 (1.12-1.29)	0.03	79.3
12	rs4760790	TSPAN8	A	0.98 (0.84-1.15)	0.83	European	1.11 (1.06-1.16)	0.14	54.2
12	rs7957197	HNF1A	T	1.02 (0.84-1.23)	0.86	European	1.14 (1.08-1.19)	0.28	15.7
15	rs7178572	HMG20A	G	1.14 (0.98-1.32)	0.08	South Asian	1.09 (1.06-1.12)	0.56	0.0
15	rs11634397	ZFAND6	G	1.02 (0.88-1.17)	0.81	European	1.11 (1.06-1.16)	0.26	21.0
15	rs2028299	AP3S2	C	1.02 (0.86-1.21)	0.80	South Asian	1.10 (1.07-1.13)	0.38	0.0
15	rs8042680	PRC1	A	1.08 (0.94-1.24)	0.28	European	1.10 (1.06-1.15)	0.80	0.0
16	rs11642841	FTO	A	0.99 (0.85-1.14)	0.86	European	1.13 (1.08-1.18)	0.09	65.5
17	rs4430796	HNF1B	G	1.08 (0.93-1.24)	0.30	European	1.14 (1.08-1.20)	0.49	0.0
20	rs4812829	HNF4A	A	1.27 (1.07-1.51)	6.80×10^{-3}	South Asian	1.09 (1.06-1.12)	0.09	65.9
23	**rs6945326**	**DUSP9**	**A**	**1.34 (1.04-1.73)**	**0.02**	**European**	**1.27 (1.18-1.37)**	**0.69**	**0.0**

Discussion

In the present study, the association of T2DM with 38 SNPs, that were previously identified and confirmed by genome wide association studies of European (32 SNPs) (1,3-9) and South Asian (6 SNPs) (2) populations, was investigated in the Saudi population (RIYADH cohort). Among the 37SNPs passing quality control measures, 8 SNPs showed significant association with T2DM at the nominal level (P<0.05) and two other SNPs showed borderline significant associations. The direction of effect of the T2DM-associated SNPs in our study population was consistent with previously reported results in other populations however, there was generally a trend for larger effect size in our population but this was not statistically significant. The SNP at TCF7L2 showed the strongest association signal and the largest effect size in our study population which is consistent with results reported in other populations (4,5,7,8).

conclusion

In conclusion we have shown for the first time that variants at WFS1, JAZF1, CDKN2A/B, TCF7L2, KCNQ1, HNF4A, and DUSP9 are associated with T2DM in the Saudi population but further larger studies will be required to confirm these findings in other Middle Eastern populations with high T2DM prevalence and to identify other T2DM-susceptibility loci..

Acknowledgement

The authors are grateful to Prince Mutaib Chair for Biomarkers of Osteoporosis Research, King Saud University, Riyadh Saudi Arabia for technical and funding support.

References

1. Grant,S.F., Thorleifsson,G., Reynisdottir,I., Benediktsson,R., Manolescu,A., Sainz,J., Helgason,A., Stefansson,H., Emilsson,V., Helgadottir,A. et al (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat.Genet., 38, 320-323.
2. Kooner,J.S., Saleheen,D., Sim,X., Sehmi,J., Zhang,W., Frossard,P., Been,L.F., Chia,K.S., Dimas,A.S., Hassanali,N. et al (2011) Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci. Nat.Genet., 43, 984-989.
3. Rung,J., Cauchi,S., Albrechtsen,A., Shen,L., Rocheleau,G., Cavalcanti-Proenca,C., Bacot,F., Balkau,B., Belisle,A., Borch-Johnsen,K. et al (2009) Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat.Genet., 41, 1110-1115.
4. Scott,L.J., Mohlke,K.L., Bonnycastle,L.L., Willer,C.J., Li,Y., Duren,W.L., Erdos,M.R., Stringham,H.M., Chines,P.S., Jackson,A.U. et al (2007) A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science, 316, 1341-1345.
5. Sladek,R., Rocheleau,G., Rung,J., Dina,C., Shen,L., Serre,D., Boutin,P., Vincent,D., Belisle,A., Hadjadj,S. et al (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature, 445, 881-885.
6. Unoki,H., Takahashi,A., Kawaguchi,T., Hara,K., Horikoshi,M., Andersen,G., Ng,D.P., Holmkvist,J., Borch-Johnsen,K., Jorgensen,T. et al (2008) SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat.Genet., 40, 1098-1102.
7. Voight,B.F., Scott,L.J., Steinthorsdottir,V., Morris,A.P., Dina,C., Welch,R.P., Zeggini,E., Huth,C., Aulchenko,Y.S., Thorleifsson,G. et al (2010) Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat.Genet., 42, 579-589.
8. Zeggini,E., Scott,L.J., Saxena,R., Voight,B.F., Marchini,J.L., Hu,T., de Bakker,P.I., Abecasis,G.R., Almgren,P., Andersen,G. et al (2008) Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat.Genet., 40, 638-645.
9. Zeggini,E., Weedon,M.N., Lindgren,C.M., Frayling,T.M., Elliott,K.S., Lango,H., Timpson,N.J., Perry,J.R., Rayner,N.W., Freathy,R.M. et al (2007) Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science, 316, 1336-1341.