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Genetic polymorphisms associated with type 2 diabetes in the Arab world: A systematic review and meta-analysis

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ABSTRACT

Aims: T2DM reach epidemic levels in the Arab countries. In this study, we aimed to perform a systematic review and meta-analysis to underline the susceptibility genetic profile of Arab patients with T2DM that result from SNPs.

Methods: We searched four literature databases (PubMed, Scopus, Science Direct and Web of Science) through January 2019. We included all SNPs in candidate genes with an OR > 1 that were associated with T2DM among Arab patients with T2DM. Statistical programs such as software Review Manager (Version 5.02) and STATA (Version 15.1) were used. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with a random effects model or a fixed effect model depending on the heterogeneity among studies. I^2 statistics and Egger's tests were performed to assess heterogeneity and publication bias.

Results: Out of 2245 studies, 47 were used for meta-analysis. We captured 31,307 cases and 26,464 controls in which we collected 71 SNPs in 32 genes. A pooled meta-analysis demonstrated 24–69% increase in T2DM risk. Among the 57 SNPs (in 32 genes) that were not included in the meta-analysis, the OR for diabetes ranged from 1.02 to 5.10, with a median of 1.38 (interquartile range 1.33–2.09). Ten studies examined the association between the *TCF7L2* polymorphism rs7903146 and T2DM, leading to an aggregated OR of 1.34 (95%CI 1.27–1.41).

Conclusion: The genetic profile that confer susceptibility to T2DM in Arab patients is diverse. This study may serve as a platform for designing a gene panel for testing the susceptibility to T2DM.

1. Introduction

The global prevalence of diabetes is steadily increasing, with an estimated 425 million adults living with diabetes in 2017; this number of adults with diabetes is expected to reach 629 million by 2045, with an increase of 48% (www.IDF.org). In the Middle East and North Africa (MENA) region, 18 out of 21 countries are populated by Arabs; this demographic has the second

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highest incidence of diabetes worldwide, with 39 million people living with diabetes in 2017 and a projected to increase of 110% by 2045 (www.IDF.org). Arab countries comprise 22 countries (Bahrain, Kuwait, Oman, Saudi Arabia, Qatar, and United Arab Emirates, Algeria, Egypt, Iraq, Jordan, Lebanon, Libya, Morocco, Palestine, Somalia, Sudan, Syria, Tunisia, Comoros, Djibouti, Mauritania, and Yemen) that vastly diverse, both socioeconomically and geographically [1,2].

Type 2 diabetes (T2DM) is a complex disease that is caused by a complex interaction between genetic and environmental factors [3]. Genetic factors are believed to play a major role in the pathogenesis of T2DM with a heritability rate that varies across different ethnic groups and is estimated to range from 20% to 80% [4]. A positive family history of affected first degree relatives with T2DM increases the risk of developing T2DM by ~3 times [5]. The concordance rate of T2DM among monozygotic twins was reported at 70%, compared to 20%–30% among dizygotic twins, indicating that genetic factors contribute to the susceptibility of individuals to T2DM [6]. Many candidate genes that are associated with susceptibility to T2DM were mapped across the genome through high-throughput SNP genotyping technology, and numerous SNPs in over 222 candidate genes were reported to be significantly associated with T2DM [7].

T2DM is considered to have reached epidemic proportions throughout Arab countries [1], and genetics are believed to play an important role in the pathogenies of diabetes and may contribute to disease incidence in Arabs possibly due to the unique genetic architecture of Arabs which renders them susceptible diabetes [1]; furthermore, the majority of Arab T2DM patients are believed to be undiagnosed [8]. Therefore, we aimed to conduct a systematic review and meta-analysis to investigate the significantly associated single nucleotide polymorphisms (SNPs) in candidate genes that are associated with susceptibility to and development of T2DM among patients from 22 Arab countries.

2. Methods

2.1. Search strategy

We conducted a systematic review of all published peer-reviewed research articles that reported patients with T2DM in any of the 22 Arab countries to capture the (SNPs) that were reported to be significantly associated with Arab patients with T2DM. We searched four literature databases: PubMed, Scopus, Direct Science and Web of Science through January 2019. The search terms were "Type 2 diabetes" OR "T2D" OR "T2DM" OR "NIDDM" OR "noninsulin dependent diabetes mellitus". Each term was used individually in combination with one of these terms: "genetic" OR "mutation" OR "variant" OR "SNP" OR "genotype" OR "genes" OR "gene", with each name of the 22 Arab countries. For example, "Type 2 diabetes" AND "variant" AND "Qatar".

2.2. Study selection and data extraction

Our selection criteria included (i) research articles that were published in only a peer-reviewed journal, (ii) articles that reported on only T2DM in Arab countries, (iii) articles that included genetic association data, (iii) genetic variants that were significantly associated with T2DM Arab patients and had an odds ratio (OR) >1. All articles that did not meet our inclusion criteria were excluded.

Our search strategy resulted in 22,45 studies that were exported to Endnote X8, after which duplicates were removed. Of these, 167 studies were selected for further full-article screening according to our selection criteria (Fig. 1). The selection was quality controlled by five scientists (AQ, FN, HA, NB and RB) independently to assure that the data were captured correctly. A consensus through discussion was reached to collect all the information related to the SNPs that were significantly associated with T2DM with an OR > 1 among Arab patients (Tables 1). We captured all the data related to the genes implicated, SNPs, number of cases vs number of controls, ORs, and 95%CIs (Table 1).

2.3. Statistical analysis

Meta-analyses were conducted using Stata version 15.1. We used a fixed effects model to summarize study estimates (odds ratios and 95% confidence intervals) when there were two or more studies for a variant. Heterogeneity among the results of the studies was assessed with the I^2 statistic. In the case of between-study heterogeneity ($I^2 > 50\%$), the random effect model was applied instead. Publication bias was assessed using a funnel plot and Egger's test if the number of studies included in a meta-analysis was ≥10.

3. Results

Our initial search yielded 2245 citations, of which 47 met our inclusion criteria and were therefore included in our meta-analysis (Fig. 1). The 47 studies included in the meta-analysis were conducted in 13 different Arab countries. All of the studies were case-control studies in which the total number of cases was 31,307 cases and the number of controls was 26,464. The number of captured SNPs was 71, which mapped onto 32 different genes (Table 1, Fig. 2). No genetic data were captured from 9/22 Arab countries (Camaros Island, Djibouti, Jordan, Kuwait, Libya, Syria, Bahrain, Somalia and Yemen). Most of the genetic studies captured populations in Tunisia (n = 10), Saudi Arabia (n = 10), Lebanon (n = 5), Morocco (n = 5), Egypt (n = 4), Qatar (n = 2).

The *Transcription Factor-7-Like 2* (*TCF7L2*) gene was the most reported among Arab patients with T2DM, and eight different SNPs were found in nine Arab countries. Interestingly, all variants of this gene were intronic. The most common variant detected among Arab patients was *TCF7L2:* c.382-41435C > T (rs7903146), which was identified in 16 different studies, followed by the variant *TCF7L2:* c.483 + 9017G > T (rs12255372), which was reported in eight Arab countries (Table 1). In the *CDKAL1* gene, 17 SNPs were identified in four Arab countries (Morocco, Lebanon, Oman, and Tunisia) that were significantly associated with Arab patients with T2DM (Table 1, Fig. 3, and Supplementary Fig. 1).

Fourteen SNPs were eligible for meta-analysis based on the number of studies per SNP (Supplementary Fig. 1). Of these 14

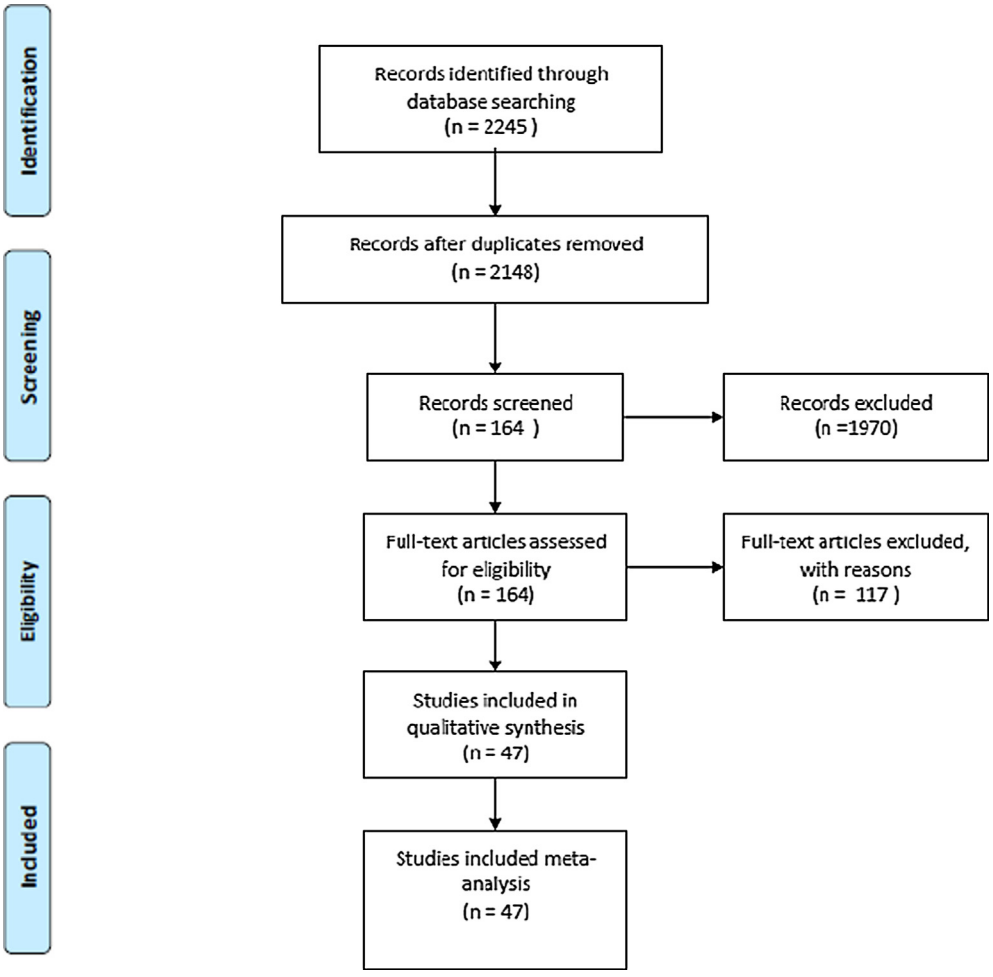

Fig. 1 – Study selection.

meta-analyses, five studies included five SNPs in *TCF7L2* (rs7903146, rs12255372, rs4506565, rs12243326, and rs7901695); two studies included two SNPs in *CDKAL1* (rs7754840 and rs10946398); and one study included one SNP for each of the genes *CDKN2A/B* (rs10811661), *KCNJ11* (rs5219), *FTO* (rs9939609), *IGF2BP2* (rs1470579), *MTHFR* (rs1801133), *SLC30A8* (rs13266634), and *HNF1A* (rs7957197) (Supplementary Fig. 1). The pooled meta-analysis for the individual 14 meta-analyses is shown in Fig. 3 and demonstrates the significant risk association between these 14 SNPs and developing T2DM.

We were able to perform publication bias for only one eligible SNP, which was reported in more than ten studies (Fig. 4). Although the funnel plot suggested no publication bias, Egger's test found otherwise (p = 0.014). No heterogeneity was found in any of the meta-analyses. Fig. 5 shows the ORs for diabetes among the 57 studies (32 genes, 59 SNPs) not included in the meta-analysis. The ORs for diabetes among these studies ranged from 1.02 to 5.10, with a median of 1.38 (interquartile range 1.33–2.09).

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to analyze the risk-associated gene polymorphisms with T2DM among Arab patients in case-control studies. We captured all gene variants that were reported to be significantly associated with T2DM among Arab adults. The number of cases was 31,307, and the control was 26,464. We captured 71 SNPs in 32 genes (Table 1). Gene variants in 32 genes were found to increase the risk of T2DM by 30–40% based on the median of the OR compared to individuals without diabetes. We conducted 14 meta-analyses on 14 SNPs for nine different genes (Supplementary Fig. 1) that demonstrated the potential risk of developing T2DM. The pooled meta-analysis for the 14 different analyses indicated that there was no heterogeneity in the captured studies, and the pooled effect of the SNPs was potentially conferring significant risk, indicating that all captured SNPs potentially conferred the risk of developing T2D. Most of the ORs were in the range of 1.3–2.0, indicating a significant association (Supplementary Fig. 1). The most reported gene was the *TCF7L2* gene (n = 35), with ten different SNPs (rs7903146; n = 15, rs12255372; n = 8, rs4506565; n = 5, rs12243326; n = 2, rs7901695; n = 2, rs7901695; n = 2, rs7901695; n = 2, rs35198068; n = 1, rs10885409; n = 1, and rs34872471; n = 1). *CDKAL1* was reported with 16 SNPs in six different studies (n = 16). Although the *CDKAL1* gene was reported in fewer studies (n = 6), it represented the gene where most of the SNPs were captured (17 SNPs were reported for this gene).

Table 1 – Significant associated variants with T2DM among Arab populations.

Reference	Gene	SNP#	Variant	Country	Cases	Control	OR	95% CI
[9]	*TCF7L2*	rs7903146	C > T	Palestine	219	114	3.34	1.99–5.60
[38]				UAE	464	415	1.73	1.17–2.54
[39]				Lebanon	691	919	1.34	1.20–1.60
[40]				Lebanon	750	918	1.38	1.20–1.59
[41]				Lebanon	1388	1902	1.31	1.19–1.45
[42]				Qatar	1124	590	2.17	1.291–3.649
[43]				Tunisia	1446	942	1.19	1.04–1.37
[14]				Algeria	76	675	1.55	1.09–2.20
[44]				Oman	992	992	2.94	1.16–1.83
[45]				Tunisia	884	513	1.33	1.04–1.70
[40]				Tunisia	1470	838	1.36	1.18–1.5
[46]				Egypt	180	210	1.62	1.17–2.25
[47]				Sudan	240	128	1.69	1.21–2.38
[71]				Saudi Arabia	1166	1235	1.55	1.33–1.80
[46]		rs12255372	G > T	Egypt	180	210	2.06	1.45–2.93
[47]				Sudan	240	128	1.70	1.20–2.41
[39]				Lebanon	691	919	1.68	1.45–1.93
[48]				Saudi Arabia	359	351	1.347	1.0454–1.7362
[49]				Tunisia	900	883	1.26	1.02–1.55
[50]				UAE	95	85	1.59	1.11–2.27
[48]		rs4506565	A > T	Saudi Arabia	359	351	1.60	1.1472–2.2498
[41]				Lebanon	1388	1902	1.31	1.18–1.44
[39]				Lebanon	691	919	1.43	1.20–1.82)
[42]				Qatar	1124	590	2.43	1.409–4.195
[49]				Tunisia	900	883	1.39	1.13–1.71
[39]		rs12243326	T > C	Lebanon	691	919	1.50	1.30–1.73
[49]				Tunisia	900	883	1.36	1.11–1.68
[41]		rs7901695	T > C	Lebanon	1388	1902	1.30	1.18–1.43
[39]				Lebanon	691	919	1.38	1.20–1.60
[41]		rs34872471	T > C	Lebanon	1388	1902	1.32	1.19–1.46
		rs35198068	T > C				1.31	1.19–1.45
[51]		rs10885409	T > C	UAE	272	216	1.9	1.127–3.461
[41]	*CDKAL1*	rs7754840	G > T	Lebanon	1388	1902	1.34	1.21–1.49
			G > C				1.32	1.21–1.49
[52]			G > A	Morocco	521	423	1.20	0.99–1.46
[53]			G > C	Lebanon	630	792	1.44	1.23–1.68
[41]		rs7756992	A > T		1388	1902	1.34	1.21–1.49
[53]			A > G		630	792	1.35	1.15–1.59
[43]				Tunisia	1446	942	1.20	1.03–1.39
[41]		rs7766070	C > A	Lebanon	1388	1902	1.38	1.24–1.54
		rs9348441	T > A				1.38	1.24–1.53
		rs35261542	C > A				1.38	1.23–1.53
		rs7451008	T > C				1.37	1.23–1.53
		rs1569699	T > G				1.33	1.21–1.48
		rs9368222	C > A				1.36	1.22–1.52
		rs9350271	G > T				1.33	1.2–1.47
		rs10946396	G > A				1.33	1.2–1.47
		rs6456369	T > A				1.33	1.2–1.47
		rs6456368	T > C				1.35	1.21–1.5
		rs35456723	T > G				1.35	1.21–1.5
		rs9295474	C > T				1.35	1.21–1.5
		rs6456367	T > A		1388	1,902	1.34	1.21–1.49
		rs7752780	G > A		1388	1902	1.34	1.21–1.49
[52]		rs10946398	A > C	Morocco	521	423	1.21	0.99–1.47]
[44]				Oman	992	294	1.44	1.15–1.80
[44]	*CDKN2A/B*	rs10811661	T > C	Oman	992	294	1.4	1.06–1.84
[43]				Tunisia	1446	942	1.20	1.03–1.39
[54]		rs10757274	A > G	Saudi Arabia	2576	2074	1.022	0.932–1.121
[55]	*KCNJ11*	rs5219	E23K	Tunisia	250	267	1.6	1.14–2.27
[49]				Tunisia	900	883	1.47	1.19–1.82
[40]				Tunisia	1470	838	1.27	1.09–1.47
				Lebanon	1470	838	1.07	0.91–1.25

Table 1 – (continued).

Reference	Gene	SNP#	Variant	Country	Cases	Control	OR	95% CI
[44]				Oman	992	294	1.74	1.37–2.22
[56]				Mauritania	135	135	2.08	1.09–3.97
[57]				Saudi Arabia	550	335	1.7	1.3–2.2
[58]	*CAPN10*	rs3792267	G > A	Tunisia	331	403	2.38	1.05–5.48
[59]		rs3842570	g.13130_13161dup	Tunisia	917	748	1.35	1.08–1.68
[47]		rs2975760	T > C	Sudan	240	128	2.38	1.09–5.26
[17]	*FTO*	rs17817449	T > G	Iraq	400	400	2.21	1.64–2.96
[19]		rs1421085	T > C	Tunisia	163	193	1.61	1.14 – 2.26
[18]		rs9939609	T > A	Palestine	281	118	1.92	1.09–3.29
[17]				Iraq	400	400	1.63	1.20–2.20
[40]	*IGF2BP2*	rs1470579	A > C	Lebanon	544	606	1.66	1.42–1.94
[43]				Tunisian	1446	942	1.41	1.07–1.85
[60]				Lebanon	544	606	1.36	1.14–1.61
[60]		rs440960	A > G	Lebanon	544	606	1.66	1.34–1.90
[61]	*MTHFR*	rs1801133	A > C	Lebanon	252	309	1.34	0.84–2.14
			C > T	Lebanon	252	309	2.43	1.48–3.99
[62]				Morocco	282	232	1.39	1.07–1.81
[43]	*KCNQ1*	rs231362	A > G	Tunisia	1446	942	1.15	1.00–1.32
[63]		rs2237892	C > T	Lebanon	995	1076	2.41	2.16–3.01
[63]		rs2237895	A > T	Lebanon	995	1076	1.21	1.04–1.38
[64]	*SLC30A8*	rs13266634	C > T	Tunisia	331	403	1.59	1.14–2.01
[40]				Tunisia	1470	838	1.37	1.15–1.62
[49]				Tunisia	900	883	1.31	1.02–1.67
[65]				Saudi Arabia	90	95	7.429	0.828–66.62
[66]	*TNF-A*	rs1800629	G > A	Morocco	307	244	1.82	1.14–2.91
[64]	*LOC387761*	rs7480010	G > A	Tunisia	331	403	2.41	1.76–3.29
[67]	*SLMAP*	rs17058639	C > T	Qatar	238	104	2.08	0.77–5.60.
[43]	*WFS1*	rs10010131	A > G	Tunisia	1446	942	1.43	1.05–1.92
[68],	*GLUT1*	rs841853	A > C	Tunisia	273	343	2.4	1.7–3.4
		rs710218	T > A	Tunisia	273	343	2.5	1.3–4.7
		rs841847	T > C	Tunisia	273	343	1.9	1.4–2.7
[49]	*POLI*	rs488846	T > C	Tunisia	900	883	1.40	1.01–1.96
[20]	*ADIPOQ*	rs16861194	A > G	Tunisia	211	110	1.65	1.30–2.09
		rs17300539	G > A		200	114	1.62	1.28–2.04
		rs266729	C > G		405	279	1.37	1.18–1.60
		rs1063538	T > C		436	334	1.18	1.03–1.36
[21]		rs2241766	T > G	Egypt	296	209	1.92	1.32–2.79
		rs17300539	G > A		296	209	4.21	1.85–9.54
[38]	*MC4R*	rs6567160	T > C	UAE	464	415	1.70	1.14–2.54
[69]	*APLN*	rs3115757	G > C	Egypt	95	56	1.42	1.19, 1.70
[70]	*PPARG*	rs1801282	C > G	Egypt	37	37	3.4	1.7–6.7
	GCKR	rs780094	T > C	Egypt	37	37	4.1	1.9–8.5
	PTGS1	rs5788	C > A	Egypt	37	37	4.1	1.8–9.3
	EXT2	rs3740878	T > C	Egypt	37	37	5.1	1.8–14.5
	FCGRA2	rs1801274	A > G	Egypt	37	37	3.2	1.1–9.5
	STAT4	rs7574865	T > G	Egypt	37	37	2.7	1.3–5.5
[43]	*HNF1A*	rs7957197	T > A	Tunisia	1446	942	1.27	1.06–1.49
				Morocco	1193	1055	1.27	1.06–1.49
[71]	*HNF4A*	rs4812829	G > A	Saudi Arabia	1166	1235	1.27	1.07–1.51
[72]	*NAT1*	rs1041983	G > A		186	183	2.09	0.46–9.45
[65 73]	*JAZF1*	rs864745	T > C		400	400	2.2	1.4–3.4
[74]	*VDR*	rs1544410	C > T		368	259	1.7	(1.2, 2.4)
		rs731236	A > G		368	259	1.3	0.90–1.9
[75]	*IRS-1*	rs1801278	C > T		367	380	1.789	1.01–3.17
[76]	*ENPP1*	rs1044498	C > A	Morocco	503	412	1.55	1.16–2.07

The *TCF7L2* gene was the most reported among Arab patients with T2DM, and it was reported among patients from ten Arab countries (Palestine, UAE, Lebanon, Qatar, Tunisia, Sudan, Algeria, Oman, Egypt and Saudi Arabia) that are socioeconomically diverse. rs7903146 (c.382–41435 C > T), which is the most predominant intronic variant that represents a 3-fold increased risk for T2DM among Arab patients [9], was reported in 11 different studies (Table 1) and was reported to significantly confer susceptibility to T2DM (Fig. 3 and Supplementary Fig. 1). Thus, rs7903146 is considered to be the most significant risk variant for developing T2DM to date [10]. A recently published meta-analysis suggested that

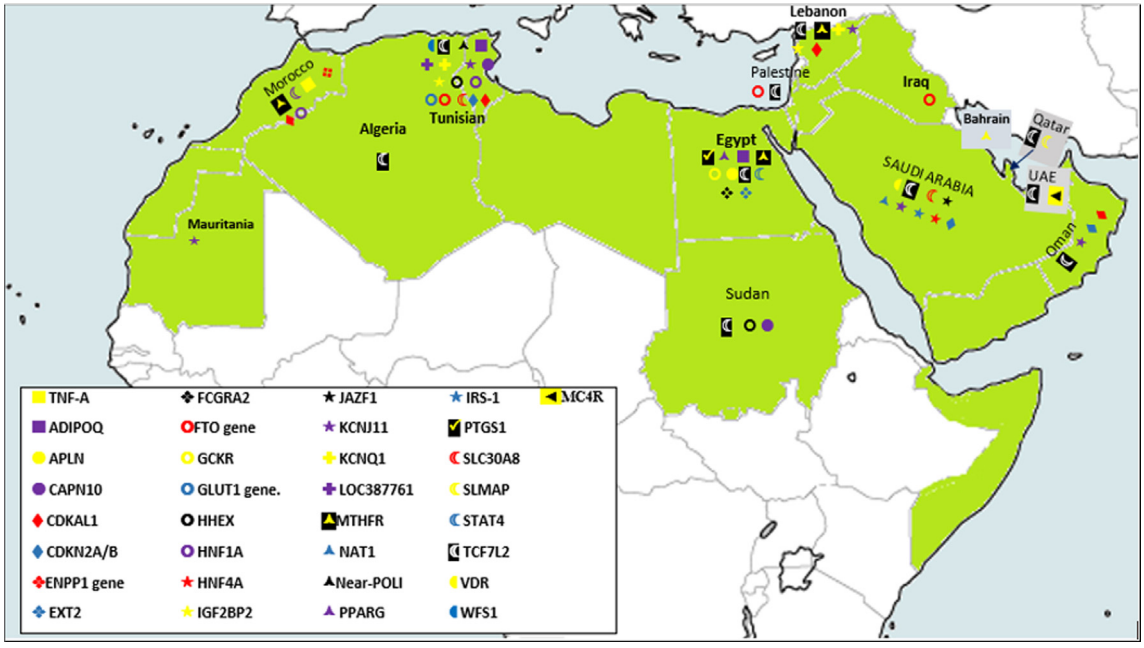

Fig. 2 – Distribution of associated genes with T2DM among Arab countries.

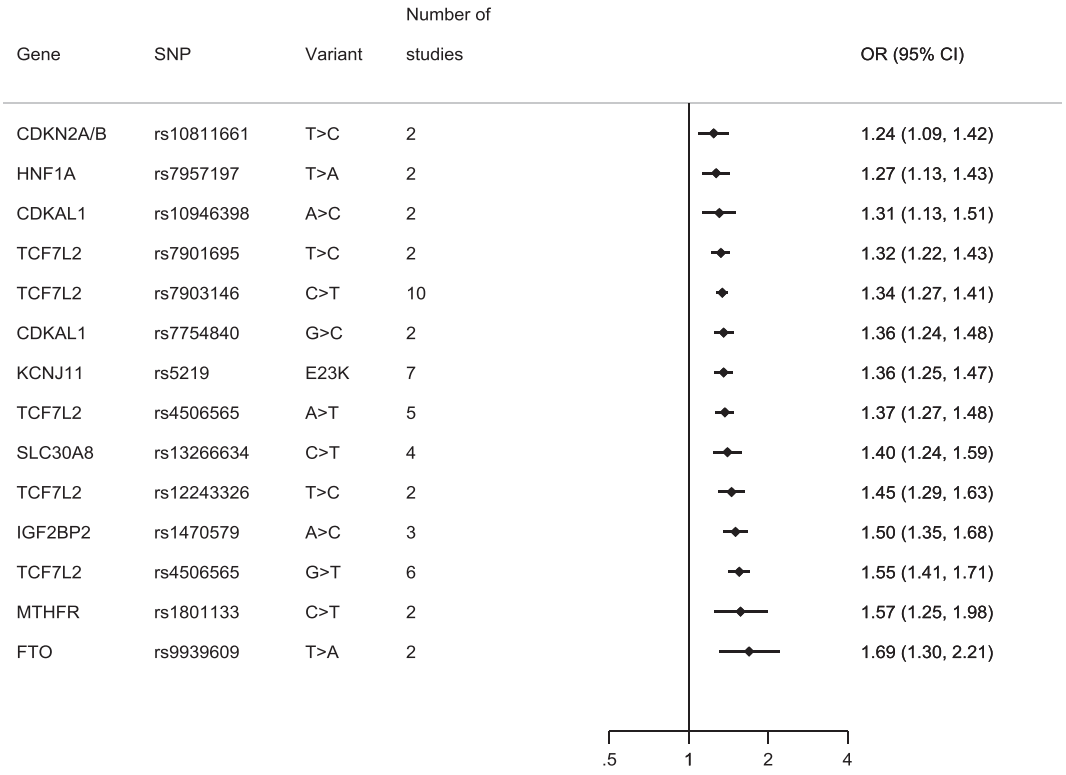

Fig. 3 – Summary of 14 individual meta-analyses.

rs7903146 was also significantly associated with T2DM in Caucasians, East Asians, South Asians and other ethnic groups [11]. Interestingly, Ding et al. studied a smaller sample size than the one used in this study; however, the aggregated ORs for T2DM were almost the same between the two studies.

TCF7L2 is a member of the TCF family and acts as a transcription factor in a bipartite fashion (β-catenin/TCF) [12]; TCF7L2 plays an important role in regulating glucose metabolism in both the liver and pancreas [13]. TCF7L2 is also an integrated signaling regulator of adipogenesis and is reported to reduce

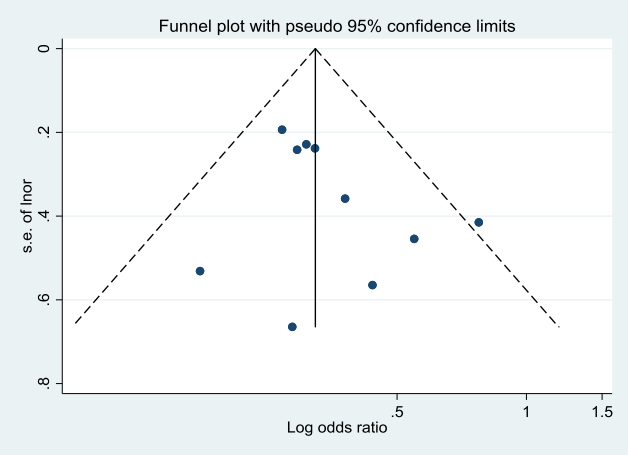

Fig. 4 – Publication bias funnel plot.

glucose-dependent insulin secretion and beta cell function [14]. Therefore, changes in the structure of TCF7L2 due to genetic variants might cause adipocyte dysfunction and could be a cause of T2DM [15]. The *TCF7L2* gene is considered the most common susceptible gene for T2DM among various ethnic groups worldwide.

We captured seventeen variants in the *CDKAL1* gene in T2DM Arab patients in six individual studies that reported in six Arab countries (Lebanon, Morocco, Tunisia, Oman, Mauritania, and Saudi Arabia) that are geographically and socioeconomically diverse; interestingly, most of the SNPs were found in Lebanon (16/17), with rs7756992 (n = 2), rs7754840 (n = 4) and rs10946398 (n = 2) reported in more than a single study (Table 1). A comprehensive meta-analysis investigated 21 studies for rs7756992, 17 studies for rs7754840 and ten studies for rs10946398 of the *CDKAL1* gene, and their effect on the genetic susceptibility to T2DM found that these three SNPs showed significant associations with T2DM among different ethnic groups [16].

We found three significantly mutated genes among our T2DM patients' cohorts that were associated with obesity (*ADIPOQ, FTO,* and *MC4R*). Three SNPs were mapped to the *FTO* gene (n = 3) among Iraqi, Tunisian, and Palestinian patients [17–19]. We captured six SNPs in two studies (n = 2) in the *ADIPOQ* gene: four were identified among Tunisian T2DM patients (n = 1) [20], and two SNPs were captured among Egyptian patients (n = 1) [21]. We captured one SNP in the obesity gene *MC4R* (rs6567160); this SNP was considered the most significant SNP in a meta-analysis of BMI that was performed on 71,412 individuals among African Americans [22]. The *FTO* gene plays an important role in controlling energy consumption and feeding behavior, and it is described as "the first locus unequivocally associated with adiposity" [23]. The *ADIPOQ* gene is exclusively expressed in adipose tissues and is involved in fatty acid breakdown in the liver and muscles and in regulating glucose levels [24], stimulating the consumption of energy. The *MC4R* gene is considered to be the most common cause of monogenic obesity [25]. Genetic variants in the *FTO*, *ADIPOQ*, and *MC4R* genes are associated with obesity, which represents a major risk of developing T2DM [26]. According to the WHO, there is a high prevalence of obesity among Arabs, especially the Arabs of the Gulf, mainly in Kuwait, United Arab Emirate, and Saudi Arabia [27].

The *KCNJ11* gene contributes to the formation of four out of the eight subunits of the ATP-sensitive potassium (K-ATP) channel of the pancreatic beta cells that secrete insulin. Our search strategy found *KCNJ11*-rs5219 in six studies (n = 6) among Arab patients belonging to five countries (Tunisia, Mauritania, Oman, Lebanon, and Saudi Arabia). Numerous reports have reproduced the association of SNPs in the *KCNJ11* gene with susceptibility to T2DM; more specifically, a *meta*-analysis and 24 association studies reiterated a strong association between the rs5219 polymorphism and susceptibility to T2DM, whereas 21 studies did not replicate this relationship [28].

The *HNF1A* and *HNF4A* genes are known to be associated with monogenic diabetes of the young (MODY) genes [29,30]. Among Arab patients, the variant HNF1A rs7957197 was detected (n = 1) among T2DM patients from Tunisia and Morocco. Our search identified the variant *HNF4A*: rs4812829 in Saudi Arabian patients with T2DM; this variant was previously identified as conferring a significant risk for patients with T2DM from Asia and Europe [31]. These two genes are involved in beta cell functions. Polymorphisms in these genes that do not cause MODY were found to be associated with susceptibility to T2DM in different ethnic groups. Mutant forms of *HNF1A* and *HNF4A* were reported to decrease secretion of insulin [29,30].

We used STRING database (https://string-db.org/) to demonstrate the potential interaction between the genes we captured, the genes were transferred to Cytoscape v3.7.1 (https://cytoscape.org/) for demonstration (Fig. 6A), and we found massive network of interactions of the genes, suggesting overlapping functions. We conducted a PANTHER classification analysis with the 32 genes [32], we found that these genes are contributing to diverse number of molecular functions (Fig. 6B) and different pathway involvement (Fig. 6C), including, glucose levels and insulin regulation pathways; for example, the *GLUT1* gene plays an important role in glucose transport across plasma membranes [33,34]. The IRS-1 plays a role in insulin signal transduction. The SLC30A8 is important in glucose homeostasis, and *CAPN10* may play a role in insulin-stimulated glucose uptake, and the *IGF2BP2* may play a role in glucose hemostasis and beta cell function [35]. These genes and the remainder captured genes in our study seem to have a complex network of interactions, as shown in Fig. 6, and several or a few might take part in the pathogenesis of T2DM; these putative interactions merit further investigation.

We performed 14 meta-analyses for 14 different SNPs that were detected in nine genes to investigate the association between these SNPs and T2DM susceptibility profiles among Arabs; the ORs ranged from 1.19 to 7.43. Pooled estimates for the summary of the 14 meta-analyses showed that these SNPs are associated with risk, and no publication bias was observed; the publication bias plot showed symmetry in the publications (Fig. 4). This was done only for one SNP that

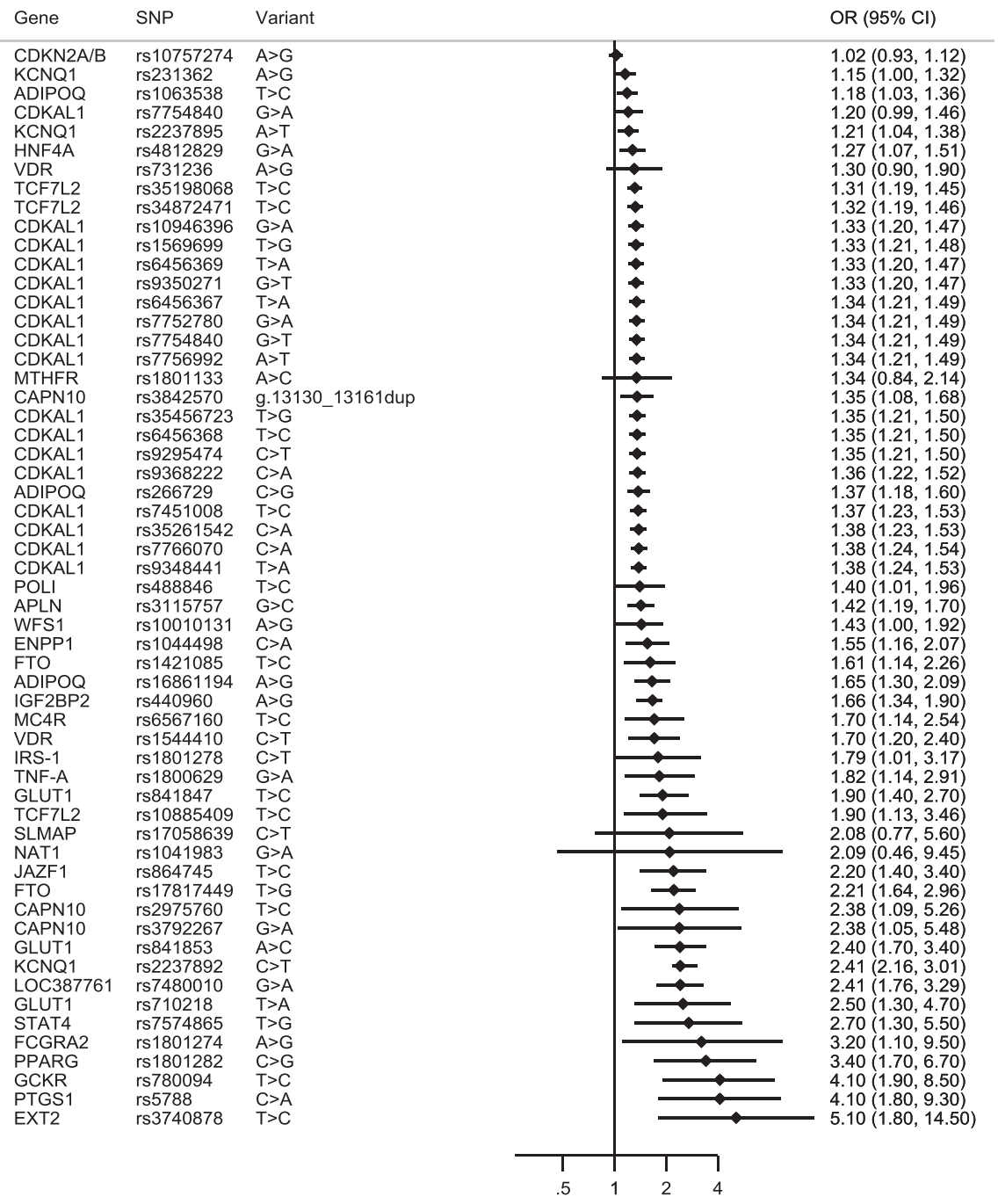

Fig. 5 – Odds ratio (95% CI) for T2DM according to the SNPs in the Arab countries. All the single studies which are not meta analyzed are presented in this Figure.

satisfied the publication bias criteria when only the ten or more studies that we could assess the publication bias for were considered.

We encountered several limitations in our study. First, there are a limited number of genetic epidemiological studies about T2DM in the Arab world and therefore we could not perform a sensitivity analysis to confirm the reliability and stability of the meta-analysis. Second, there was a lack of a comprehensive publicly accessible diabetes registry. Third, we were not able to perform a publication bias analysis because most of the SNPs were found in less than ten publications.

It seems that Arabs share susceptibility alleles with other ethnic groups. It surprised us that most of the studies were conducted in Lebanon and Tunisia, while Kuwait, Saudi Arabia, Egypt have the greatest T2DM prevalence. According to the last report from the IDF, obesity rates in Arabs are one of the highest in the world. Therefore, we think the current efforts to understand the Arab genome [36,37] will help in characterizing Arab patients with T2DM and resultant

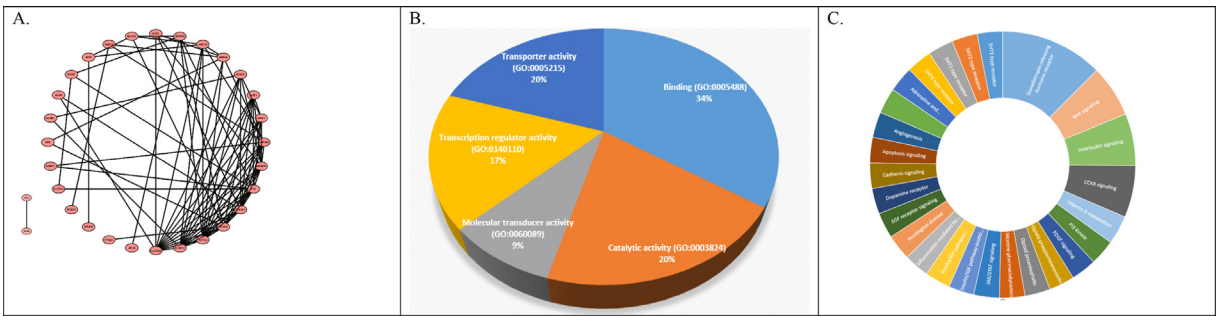

Fig. 6 – Bioinformatics analyses of the 32 genes captured in this study. (A) The potential protein-protein interactions using both STRING and Cytoscape. (B) Molecular functions and (C) Pathway analyses using PANTHER.

analyses are expected to identify Arab-specific variants that might be important in the molecular pathology of T2DM and might contribute to identifying meaningful genotype-phenotype correlations. These studies might contribute to disease prognosis and disease management in the future.

In conclusion, we collected 71 SNPs that were reported in case-control studies that are significantly associated with Arab patients with T2DM that belong to 13 Arab countries. We performed 14 meta-analyses for 14 different SNPs that were captured in nine different genes, and we combined these 14 meta-analyses in a single, representative meta-analysis. Although the pooled meta-analysis of the 14 SNPs that were captured in nine different genes is statistically powerful, the number of studies that evaluate such combined effects is considered to be small. Compared to the magnitude of the problem in the Arab world, there is a need for better, well-controlled epidemiological studies that serve as a base for dissecting the genetic architecture that renders Arab patients susceptible to T2DM. We were able to map the significant interaction of the affected proteins in this study; mapping is expected to positively aid molecular diagnostic technology for diabetes by developing a diagnostic panel for diabetes. However, more studies need to be performed to pinpoint the significance of these genes in contributing to the direct pathogenesis of T2DM. Therefore, this study may serve as a platform for designing a gene panel for testing the susceptibility of Arab patients to T2DM and will be helpful in global molecular diagnostic purposes.

Conflict of interest statement

All of the authors declare no conflict of interest.

Contributors

HZ: initiated and supervised the study, analyzed the data, and wrote the manuscript.

NA, FN, HA, RH, collected the data and wrote the manuscript.

ZS: performed the meta-analysis.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.037.

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