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REVIEW ARTICLE

Genetic screening for pathogenic variants in type 2 diabetes of the Arab Gulf population: A systematic review and meta-analysis

Karar N. J. Musafer[1] · Mohammad Rava[2] · Mohammed Baqur S. Al-Shuhaib[3]

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Abstract

Objective The Arab Gulf is highly vulnerable to T2DM and its serious consequences. The manner in which these populations respond to such alterations in their surroundings may largely be governed by their genetic makeup. This review aimed to screen the genetic loci candidates that are associated with T2DM to assess the most prominent one in the early diagnosis of this chronic dysfunction.

Methods Variable pieces of literature were searched to assess the association between pathogenic single-nucleotide polymorphisms (SNPs) and the onset of T2DM in the Arab Gulf countries. The effects of odd ratio (OR), sample sizes, and collaborations of the captured genes of the eligible studies were analyzed. The protocol was registered in National Institute for Health Research.

Results Twenty-seven pathogenic SNPs were identified in 16 genes that were reported in 31 articles encompassing 15,982 patients and 11,976 controls. The highest numbers of conducted research were localized in Iraq and Saudi Arabia with 39% and 32%, respectively. *HNF4A* and *TCF7L2* genes represent the most extensively studied pathogenic genes in terms of the number of individuals included and the number of T2DM-related loci, respectively. Intron SNPs exhibited the highest percentages of pathogenic loci associated with T2DM with 61%. Moderate association between the pathogenic SNPs and disease outcome was observed, but strengths and weights of association vary across studies.

Conclusion For a better understanding of the molecular etiology of T2DM, finding SNPs, and establishing a meaningful genotype-phenotype connection for complicated diabetic disorders, the cumulative relevance of identified pathogenic SNPs in Arab Gulf was shown.

Keywords Arab Gulf · Association · Etiology · Polymorphism · Risky SNPs

Introduction

Diabetes mellitus is among the most popular research trends in modern medicine, in which genetic variables play a critical role in its onset and development. Diabetes leads to major health issues and complications such as retinopathy, neuropathy, exhaustion, weight loss, microvascular and macrovascular abnormalities, nephropathy, and numerous types of cardiovascular illnesses like hypertension and atherosclerosis; diabetes affects patients' quality of life. Type 2 diabetes mellitus (T2DM), the most common type of diabetes, has a significant negative impact on patient's quality of life and places a significant financial burden on the country's healthcare system [1].

For the time being, diabetes affects more than 500 million individuals globally, accounting for more than 10.5% of the adult population [2]. The last two decades have

✉ Mohammed Baqur S. Al-Shuhaib
mohammed79@agre.uoqasim.edu.iq

Karar N. J. Musafer
karar.shahher@g.alzahu.edu.iq

Mohammad Rava
morava.ir@gmail.com

[1] Department of Pharmacy, Al–Zahrawi University College, Kerbala 56001, Iraq

[2] Faculty of Computing, Universiti Teknologi Malaysia, 81310 Skudai, Johor, Malaysia

[3] Department of Animal Production, College of Agriculture, Al-Qasim Green University, Al-Qasim, Babil 51001, Iraq

seen a significant increase in the prevalence of T2DM, which is attributed to its steady expansion, as evidenced by numerous studies [3]. The rate of T2DM prevalence has been estimated to exhibit a dangerous elevation as shown in the majority of reports that revealed that the number of T2DM patients having diabetes is estimated to be 640 million patients by the onset of 2040 [4]. Data from the WHO show that diabetes-related mortality has substantially expanded, and in the next 20 years, the number of people with diabetes is predicted to more than double. The Arab Gulf has the highest percentage (24.5%) of diabetes-related deaths in people of working age. The tenth edition of the IDF indicated that the global prevalence of diabetes has reached pandemic levels in this region. Though the association between genetic polymorphism and T2DM has been highlighted in the Arab world [5, 6], noticeable gaps of knowledge still exist in the genetic polymorphic variations that might be associated with the progression of the disease in the Arab Gulf region. Accordingly, genetic association studies of T2DM are beneficial in providing additional data that might aid in the early diagnosis and management of complications surrounding T2DM [7]. Despite the involvement of several genetic loci in the onset of T2DM, the present epidemic of this chronic complication cannot be only explained by one or a few loci [8–10]. Furthermore, the intensity of the possible association of these genetic loci may exhibit vast biological differences among populations worldwide.

The prevalence of T2DM is alarmingly high in the Arab Gulf, with some countries experiencing elevating rates of this disease. While lifestyle factors such as diet, physical activity, and obesity are known to contribute to the disease's risk [1], genetics is also believed to play a crucial role. Identifying the genetic loci candidates associated with T2DM in the Arab Gulf population is therefore essential to understanding the disease's underlying mechanisms and developing effective prevention and treatment strategies tailored to this population. Thus, it is necessary to pick up candidate genes implicated in molecular pathogenesis to find out the pathophysiological mechanisms of T2DM and to enhance its prognosis using the relevant biological markers [11].

This review aims to present a systematic review and meta-analysis of the genetic candidates most commonly associated with T2DM in the Arab Gulf region. By highlighting the potential of systems genetics, the review also seeks to identify these genes and identify the underlying mechanisms that contribute to the onset and progression of T2DM in this region. Various criteria were employed in this review to exclude the non-standardized publications in this area of expertise. This work provides a deeper understanding of the factors affecting T2DM as per their investigations in the Arab Gulf populations.

Materials and methods

Search strategy

Prior to commencing the review, we registered the International Perspective Register of Systematic Reviews (PROSPERO) protocol of the National Institute of Health (NIH) under the ID number 427938 (https://www.crd.york.ac.uk/PROSPERO/) [12]. Our study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. To conduct this systematic review, we conducted an exhaustive literature search across four electronic databases: Google Scholar, PubMed, Web of Science, and Scopus. This search encompassed articles published from the inception of each database up to February 24, 2023. In order to include as many relevant studies as possible for our current meta-analysis, we broadened our search criteria to include the following terms: "DM," "Type 2 diabetes," "genetics," and "SNPs," in conjunction with the names of the Arab Gulf countries (Bahrain, Iraq, Saudi Arabia, Oman, Emirates, Kuwait, and Qatar). The study started with the identification of potential studies, which were then screened based on their titles and abstracts. Eligibility criteria were applied, and the selected studies were included. Once extracted, they were synthesized and analyzed, and the results were reported.

Study selection

This review focused on prospective studies that investigated the relationship between single-nucleotide polymorphisms (SNPs) within genes associated with the pathogenesis of type 2 diabetes mellitus (T2DM). The definitions of the disease were derived from the International Classification of Diseases [14]. The inclusion and exclusion criteria for studies were as follows: included studies were those that examined T2DM and its association with specific SNPs. Excluded studies were those that (1) focused on type 1 diabetes mellitus (T1DM), (2) investigated gestational diabetes mellitus (GDM), (3) examined other types of diabetes mellitus, (4) were not written in English, (5) were published in non-peer-reviewed journals, and (6) were conducted outside the geographical boundaries of the Arab Gulf region.

Eligibility criteria

The full-text of published articles that fell within one or more of the following criteria was excluded from downstream analyses: (1) association analyses performed on a small population (less than 60 people in total), (2) the data of the controls that were not compatible with Hardy–Weinberg

equilibrium (HWE), (3) analyses revealed the presence of a non-pathogenic or protective association of a SNP with T2DM, (4) analyses that revealed non-significant or a borderline association with T2DM, and (5) SNPs that are not fully identified or not deposited in the dbSNP.

Data extraction

Data extraction for genes, details of the SNPs, number of patients and controls, genotyping method, *P*-value and odd ratio (OR) of significance, and the location of the conducted investigation were shown in a separate table for each considered genotype-phenotype association analysis. The extracted data were generated based on the alphabetic name of the gene. The following information was extracted from the T2DM-associated studies: the name of the gene, SNP ID, type/position of the pathogenic SNP, number of patients and controls, the genotyping method used, study area, and publication cited.

Statistical analysis

Standard meta-analysis was conducted using the R programming software environment, and their presentation was enhanced via advanced Microsoft Excel modules using the NumXL 1.68, Camel (NUMXL, Shigaco IL 60604, USA). The association between the pathogenic SNPs and T2DM in the Arab Gulf populations was conducted using pooled ORs and 95% confidence intervals (CIs). The distribution, magnitude of the effect sizes across studies, and consistency of the results were assessed by means of a bubble chart. In a bubble chart, each study was represented by a bubble, with the size of the bubble representing the weight or sample size of the study, and the position of the bubble indicating the effect size of the study. The potential cooperation of the identified genes was figured out using String-10 [15]. The String-10 data were retrieved and annotated using the Cytoscape software [16]. The Panther software was used to annotate the molecular functions of the synthesized genes and the pathways they involved [17].

Results

Our results demonstrate the importance of carefully selecting SNPs for analysis in genetic association studies. By excluding non-pathogenic and protective SNPs, our analysis was focused on those genetic variants that are more likely to contribute to disease susceptibility. It has been demonstrated that these SNPs exhibited significant association with the risk of T2DM with varying degrees of intensity.

Utilizing Google Scholar, PubMed, Web of Science, and Scopus resources ensured a thorough and extensive search for relevant studies ($n = 2340$). By searching across multiple databases, the duplicated research of the identified data was removed ($n = 520$). By conducting a comprehensive literature search on the residual articles ($n = 1820$), a diverse set of T2DM-related studies was gathered, ensuring a more representative and comprehensive body of evidence for the meta-analysis. The rigorous screening was identified as a crucial step in the review process for determining the relevance of studies for inclusion. The titles and abstracts of research articles were typically assessed to identify studies that had the potential to meet the criteria defined for the meta-analysis. Accordingly, studies that are concerned with T1DM ($n = 198$), GDM ($n = 212$), and other types of DM (68); not written in English ($n = 324$); not published in peer-reviewed journals ($n = 262$); or reported outside the border of the Arab Gulf ($n = 638$) were eliminated from further consideration. After omitting these researches, the residual number of the studies that were found within the inclusion criteria was only 116. A further layer of rigorous elimination was applied to provide as accurate as eligible data to reflect the actual association between pathogenic SNPs and T2DM in the Arab Gulf world. This elimination was represented by omitting studies conducted on small populations of less than 60 individuals ($n = 16$), their controls did not fall within HWE ($n = 13$), articles that found a protective association with T2DM ($n = 28$), articles reported non-significance association with T2DM ($n = 23$), or articles described non-fully identified SNPs due to their non-demonstrated positions or the absence of any mention for the rs number in the dbSNP ($n = 10$). Accordingly, the residual number of eligible studies that were included in the meta-analyses was found to constitute only 26 studies. The entire process is illustrated in Fig. 1, which depicts each step and the number of studies included or excluded.

Based on the results obtained from the 26 eligible articles, a total of 27 pathogenic SNPs were identified in 16 genes that were located in variable positions in the human genomes (Table 1). The potential pathogenicity of these SNPs has been indicated due to their significant association with T2DM in the Arab Gulf region. The functional potential of these SNPs has been elucidated by their involvement in diabetes development and progression through influencing several critical mechanisms, such as gene expression, protein stability, and cellular function. While ongoing research is investigating specific pathogenic SNPs linked to diabetes [18], studies in the Arab Gulf region have pinpointed 27 SNPs that could contribute to the disease's pathogenesis. These SNPs could play a role in the development of T2DM in this region. Among these SNPs, the *TCF7L2* gene holds the highest count (10 SNPs), constituting the majority of the T2DM-associated loci in the Arab Gulf. Additionally, four T2DM-related SNPs are located in the *VDR* gene, while each one of the *ADIPOQ*, *FTO*, and *KCNJII* genes encompasses three T2DM-related SNPs.

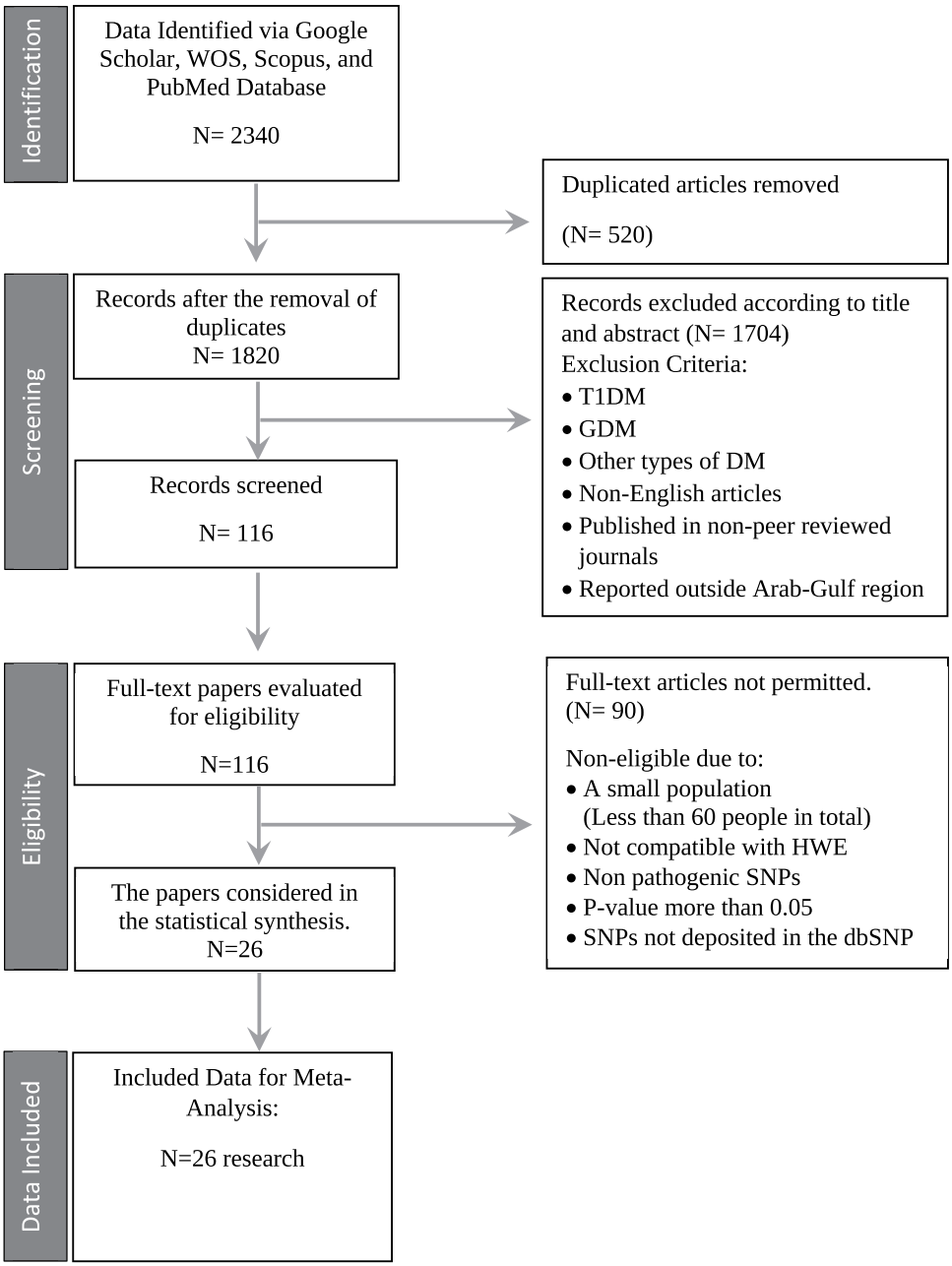

Fig. 1 PRISMA diagram for the systematic review

In contrast, the remaining 22 genes display a less frequent distribution of the rest of these SNPs. The categorization of these SNPs as pathogenic entails a complex process involving genetic analysis and an evaluation of how they may impact an individual's susceptibility to the disease. The classification of T2DM-related SNPs as pathogenic SNPs has been carried out using various rigorous and multifaceted methods aimed at understanding the potential influence of these SNPs on traits associated with T2DM. These classifications play a pivotal role in comprehending the genetic foundations of T2DM and can provide insights for personalized medicine strategies, risk assessments, and interventions for individuals at risk of developing the condition. The initial step in identifying T2DM-related SNPs in the Arab Gulf region has primarily entailed the utilization of various traditional genotyping techniques, often subsequently verified through sequencing. Additionally, computational approaches that predict the impact of SNPs on the structural and functional aspects of genes have been employed to assess how these genetic variations may affect the disease [19]. Pathogenic SNPs linked to T2DM have predominantly been identified within intron sequences, whereas other types of pathogenic SNPs have been found in various coding and noncoding sequences. The classification of SNPs as pathogenic can also help elucidate disparities in susceptibility to T2DM among the Arab Gulf population. These findings were based on a comprehensive analysis of

Table 1 The details of genes showed significant associations with diabetes mellitus type II in Arab Gulf populations

No.	Gene	SNP	Type of SNP	Patients	Controls	Genotype method	*p*-value	OR	Country	Reference
1.	*C5AR2*	rs149572881	Missense	376	175	PCR-RFLP	.009	3.7	Saudi Arabia	[20]
2.	*ACE*	rs1799752	INDEL	117	75	Allele-specific PCR	.018	3.0	Iraq	[21]
3.	*JAZF1*	rs864745	Intron variant	400	400	PCR-RFLP	.02 to .002	1.2–3.9	Saudi Arabia	[22]
4.	*ADIPOQ*	rs2241766	Silent	314	257	PCR-RFLP	.0001	5.4	Iraq	[23]
	ADIPOQ	rs17300539	Promoter	400	400	PCR-RFLP	.04 to .004	1.62-3.19	Iraq	[24]
	ADIPOQ	rs266729	Promoter	135	135	PCR-RFLP	.01	3.67	Iraq	[25]
5.	*HNF4A*	rs4812829	Intron variant	1166	1235	Allele-specific PCR	.00068	1.27	Saudi Arabia	[26]
6.	*VDR*	rs1544410	Intron variant	400	400	PCR-RFLP	.001	2.17	Iraq	[27]
	VDR	rs1544410	Intron variant	368	259	TaqMan real-time PCR	.001	2.08	Saudi Arabia	[28]
	VDR	rs731236	Silent	368	259	TaqMan real-time PCR	.030	1.43	Saudi Arabia	[28]
	VDR	rs2228570	Missense	400	400	PCR-RFLP	.024	1.30	Iraq	[29]
7.	*FTO*	rs9939609	Intron variant	120	60	ARMS-PCR	.040 to .031	Not shown	Iraq	[30]
	FTO	rs9939609	Intron variant	400	400	PCR-RFLP	.0000	1.87-5.64	Iraq	[31]
	FTO	rs17817449	Intron variant	400	400	PCR-RFLP	.0000	1.65-3.04	Iraq	[31]
8.	*SLC30A8*	rs13266634	Intron variant	89	96	Sanger sequencing	.04	7.42	Saudi Arabia	[32]
9.	*MC4R*	rs2229616	Missense	415	323	TaqMan real-time PCR	.001	1.82	Saudi Arabia	[33]
	MC4R	rs6567160	Intron variant	464	415	Genome-wide association	.0093	1.70	Emirates	[34]
10.	*TCF7L2*	rs12255372	Intron variant	351	351	Allele-specific PCR	.0213	1.34	Saudi Arabia	[35]
	TCF7L2	rs12255372	Intron variant	188	180	TaqMan real-time PCR	.03	1.47	Emirates	[36]
	TCF7L2	rs12255372	Intron variant	890	686	TaqMan real-time PCR	0.042	1.16	Emirates	[37]
	TCF7L2	rs7903146	Intron variant	106	106	Tetra ARMS-PCR	.001	2.53	Iraq	[38]
	TCF7L2	rs7903146	Intron variant	264	153	TaqMan real-time PCR	.0063	1.80	Emirates	[39]
	TCF7L2	rs7903146	Intron variant	464	415	Genome-wide association	.0056	1.73	Emirates	[34]
	TCF7L2	rs7903146	Intron variant	1124	590	TaqMan real-time PCR	.0029	1.36	Qatar	[40]
	TCF7L2	rs4506565	Intron variant	1124	590	TaqMan real-time PCR	.0037	1.33	Qatar	[40]
	TCF7L2	rs4506565	Intron variant	351	351	Allele-specific PCR	.0070	1.39	Saudi Arabia	[35]
	TCF7L2	rs10885409	Intron variant	272	216	TaqMan real-time PCR	.035	1.49	Emirates	[41]
11.	*CDKN2*A/B	rs10811661	Intron variant	400	400	PCR-RFLP	.004	1.47–4.24	Iraq	[42]
	*CDKN2*A/B	rs10811661	Intron variant	992	294	TaqMan real-time PCR	.02	1.40	Oman	[43]
12.	*LEP*	rs11761556	5′-UTR	120	100	PCR-SSCP	.01	4.58	Iraq	[44]
	LEP	rs12706832	Intron variant	120	100	PCR-SSCP	.01	2.38	Iraq	[44]
13.	*MCP-1*	rs1024611	Intron variant	135	100	Tetra ARMS-PCR	.01	3.35	Iraq	[45]
14.	*KCNJII*	rs5219	Stop-gained	40	20	PCR-RFLP	.001	7.0	Iraq	[46]
	KCNJII	rs5219	Stop-gained	992	294	TaqMan real-time PCR	.00005	1.74	Oman	[43]
	KCNJII	rs5219	Stop-gained	550	335	Real-time PCR	.0001	1.7	Saudi Arabia	[47]
15.	*SLMAP*	rs17058639	5′-UTR	238	104	TaqMan real-time PCR	.018	3.23	Qatar	[48]
16.	*IRS1*	rs1801278	Missense	376	380	PCR-RFLP	.040	1.78	Saudi Arabia	[49]
	IRS1	rs2943641	Missense	376	380	PCR-RFLP	.001	1.48	Saudi Arabia	[49]

27,958 individuals in Arab Gulf countries, which collectively encompassed 15,982 patients and 11,976 controls.

In addition to the traditional meta-analysis conducted on the relationship between SNPs and TD2M, we utilized a minor allele frequency (MAF) analysis as a quality control threshold. This was done to highlight SNPs with low MAFs, which could potentially affect the reliability of results [50]. The analysis of the data presented in Table 2 has unveiled that the majority of minor alleles in the scrutinized SNPs manifest varying levels of significant impacts on T2DM within the Arab Gulf region. Table 2 shows that more than two-thirds of the investigated SNPs are associated with these significant effects on the disease. This data underscores that the substantial effects of the studied SNPs are not confined solely to major alleles but also encompass minor alleles. Furthermore, this observation may extend to the genotypes, suggesting that multiple genotypic forms may influence T2DM, rather than just one specific genotypic form.

The *HNF4A* gene, with 1166 patients and 1235 controls investigated, had the highest number of individuals studied. However, based on the collected data, it was deduced that the *TCF7L2* gene was the most extensively screened in the Arab Gulf. Within this gene, four intron SNPs were found to exhibit significant pathogenic associations with T2DM in four countries using variable genotyping techniques. *TCF7L2*:rs7903146 showed the highest number of significant associations with T2DM in Arab Gulf countries. This is due to the presence of four different studies that referred to this association in Iraq [38], Emirates [34, 39], and Qatar [40]. *TCF7L2*:rs12255372 showed a significant association with T2DM in Saudi Arabia [35], and Emirates [36, 51]. *TCF7L2*:rs4506565 was also associated with T2DM in two studies conducted in Saudi Arabia and Emirates [41, 52]. *TCF7L2*:rs10885409 exerted a significant association with T2DM in Emirati subjects [41]. Following the extensively investigated SNPs *TCF7L2* gene, three SNPs in *ADIPOQ* and *VDR* genes exerted pathogenic association with T2DM in variable Iraqi and Saudi populations [23–25, 28, 29]. However, other listed genes showed a lower number of significantly associated SNPs with T2DM.

All over the instigated Arab Gulf countries, the highest number of studies on diabetic-related genes were found in Iraq with 39%, which was followed by Saudi Arabia with 32% (Fig. 2a). Out of sixteen screened genes that were investigated in the included researches, the highest number of investigated individuals was found in the *HNF4A* (hepatocyte nuclear factor 4 alpha) gene with 1166 patients and 1235 controls (Fig. 2b). The generated pie chart also showed that the most frequently used technique in the genotyping of these genes was polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with 34%, which was followed by TaqMan-real-time PCR with 32% (Fig. 2c), whereas each of the other genotyping techniques of PCR-single strand conformation polymorphism (PCR-SSCP) [53], genome-wide association studies (GWAS) [54], and tetra-amplification refractory mutation system (ARMS)-PCR [55] did not exceed more than 5% of T2DM assessment in Arab Gulf populations. Due to their higher frequencies of polymorphism over exon SNPs [56], intron SNPs were the most intensively investigated in terms of their association with T2DM in Arab Gulf countries with 61% (Fig. 2d), whereas SNPs in the other locations were found to exhibit lower ratios of associations with 13% of missense SNPs, 8% of stop-gained SNP, 5% of 5′UTR and silent SNPs, and 3% of INDEL SNP.

A direct comparison between OR and sample sizes was displayed in a bubble chart (Fig. 3). This comparison demonstrated the strength of the association between the two variables and indicated the level of significance of that association as determined by the *p*-value. The majority of the ORs were located between values 1 and 2, indicating a moderate association between the genetic variant and the disease outcome. Two studies have particularly high ORs [32, 46], indicating a stronger association. It is interesting to note that despite the moderate association between the genetic variant and the disease outcome in the majority of the studies, there is significant variation in the p-values. This suggested that some studies exhibited stronger statistical significance than others did, even though their ORs were found to be similar. The values of the risky ORs ranged from 1.16 in *TCF7L2*;rs12255372 [37] to 7.42 in *SLC30A8*;rs13266634 [32]. It was inferred from the bubble chart that three studies were found to exert larger effect sizes than other studies included in the analysis. These studies showed the highest weight values with OR values of 1.27 [27], 1.33 [40], and 1.16 [37], respectively. Due to these studies, the presence of moderate associations with T2DM is expected.

The *in silico* analyses of the identified T2DM-related genes indicated the presence of variable intensities of network interaction among the captured genes, which suggests the presence of numerous levels of collaboration among them. However, *KNCJ2*, *SLMAP*, and *C5AR2* genes did not exert any sort of collaboration with the presented network (Fig. 4a). The pie representations of these T2DM-related genes indicated that 36% of them were involved in binding activities. Other activities were found in fewer percentages with 18% of molecular transducer activity, 14% of catalytic and molecular function activities, and 9% of transporter and transcription regulator activities (Fig. 4b). More detailed information on the pathways these genes are involved was explained. Gonadotropin-releasing hormone receptor and p53-related pathways were found to exhibit the highest percentage with 15%. The majority of the other pathways were identified in 7%, including cadherin, Wnt, CCRK, cytokine, interleukin signaling, angiogenesis, and Alzheimer disease-presenilin pathways (Fig. 4c). Among the other T2DM-related genes, two of the insulin/IGF pathways were also identified in 7%.

Table 2 The details of minor allele frequencies of diabetes mellitus type II-related SNPs in Arab Gulf populations

No.	Gene	SNP	Variation	MAF in patients	MAF in controls	*p* value	OR	Country	Reference
1.	*C5AR2*	rs149572881	C > T	0.039	0.0133	0.0411	2.9920	Saudi Arabia	[20]
2.	*ACE*	rs1799752	D/I	0.239	0.373	0.0395	0.6410	Iraq	[21]
3.	*JAZF1*	rs864745	T > C	0.425	0.321	0.0038	1.3230	Saudi Arabia	[22]
4.	*ADIPOQ*	rs2241766	T > G	0.22	0.1175	0.0001	0.4371	Iraq	[23]
	ADIPOQ	rs17300539	G > A	0.226	0.135	0.0001	1.6759	Iraq	[24]
	ADIPOQ	rs266729	C > G	0.277	0.14	0.0017	1.9737	Iraq	[25]
5.	*HNF4A*	rs4812829	G > A	0.0428	0.024	0.001	1.7364	Saudi Arabia	[26]
6.	*VDR*	rs1544410	C > T	0.52	0.35	0.0001	1.4893	Iraq	[27]
	VDR	rs1544410	C > T	0.442	0.377	0.024	1.13	Saudi Arabia	[28]
	VDR	rs731236	A > G	0.441	0.413	0.5262	1.0689	Saudi Arabia	[28]
	VDR	rs2228570	A > C	0.71	0.43	0.0001	1.6512	Iraq	[29]
7.	*FTO*	rs9939609	T > A	0.333	0.466	0.1679	0.7143	Iraq	[30]
	FTO	rs9939609	T > A	0.2	0.3125	0.0052	0.6400	Iraq	[31]
	FTO	rs17817449	G > T	0.3625	0.2675	0.0032	1.3551	Iraq	[31]
8.	*SLC30A8*	rs13266634	C > T	0.185	0.1458	0.3866	1.2713	Saudi Arabia	[32]
9.	*MC4R*	rs2229616	C > T	0.0087	0.125	0.0001	0.0401	Saudi Arabia	[33]
	MC4R	rs6567160	G > A	0.33	0.278	0.019	1.70	Emirates	[34]
10.	*TCF7L2*	rs12255372	G > T	0.437	0.339	0.0117	1.2899	Saudi Arabia	[35]
	TCF7L2	rs12255372	G > T	0.338	0.384	0.5429	1.1103	Emirates	[36]
	TCF7L2	rs12255372	G > T	0.394	0.358	0.3290	1.0998	Emirates	[37]
	TCF7L2	rs7903146	C > T	0.406	0.292	0.014	1.65	Iraq	[38]
	TCF7L2	rs7903146	C > T	0.3725	0.4223	0.0063	1.80	Emirates	[39]
	TCF7L2	rs7903146	C > T	0.41	0.33	0.0056	1.73	Emirates	[34]
	TCF7L2	rs7903146	C > T	0.0809	0.0711	0.5838	1.1109	Qatar	[40]
	TCF7L2	rs4506565	A > G	0.0151	0.0101	0.4059	1.4872	Qatar	[40]
	TCF7L2	rs4506565	A > G	0.4094	0.4909	0.0072	1.3909	Saudi Arabia	[35]
	TCF7L2	rs10885409	T > C	0.474	0.446	0.5979	0.9413	Emirates	[41]
11.	*CDKN2*A/B	rs10811661	T > C	0.22	0.32	0.0001	1.69	Iraq	[42]
	*CDKN2*A/B	rs10811661	T > C	0.164	0.201	0.020	1.40	Oman	[43]
12.	*LEP*	rs11761556	C > A	0.625	0.37	0.008	1.93	Iraq	[44]
	LEP	rs12706832	A > G	0.383	0.61	0.006	1.75	Iraq	[44]
13.	*MCP-1*	rs1024611	A > G	0.51	0.38	0.06	1.6	Iraq	[45]
14.	*KCNJII*	rs5219	T > C	0.15	0.06	0.0004	5.00	Iraq	[46]
	KCNJII	rs5219	T > C	0.320	0.222	0.00005	1.74	Oman	[43]
	KCNJII	rs5219	C > T	0.415	0.405	0.675	1.04	Saudi Arabia	[47]
15.	*SLMAP*	rs17058639	C > T	0.341	0.403	0.009	1.76	Qatar	[48]
16.	*IRS1*	rs1801278	C > T	0.045	0.026	0.0588	1.7181	Saudi Arabia	[49]
	IRS1	rs2943641	C > T	0.299	0.223	0.0107	1.3376	Saudi Arabia	[49]

Discussion

The Arab Gulf states are a collection of Arab nations that share a Gulf as a boundary. Iraq, Kuwait, Bahrain, Saudi Arabia, Oman, the United Arab Emirates, and Qatar are the seven Arab League members in the area that share this Gulf [57]. According to the IDF database, three of the Arabian Gulf countries have occupied the highest prevalence of T2DM in 2021 with 25.5%, 17.7%, and 16.4% for Kuwait, Saudi Arabia, and Qatar respectively. Due to the significant role of the genetic factor in the disease's onset and progression, the identification of genetic variants associated with T2DM is crucial for understanding the underlying mechanisms of the disease and developing effective prevention strategies.

Our conducted meta-analyses suggest that there is a moderate association between the genetic variant and the disease outcome, but the strength of this association varies across studies. The studies with higher ORs may be particularly important for further investigation, as they

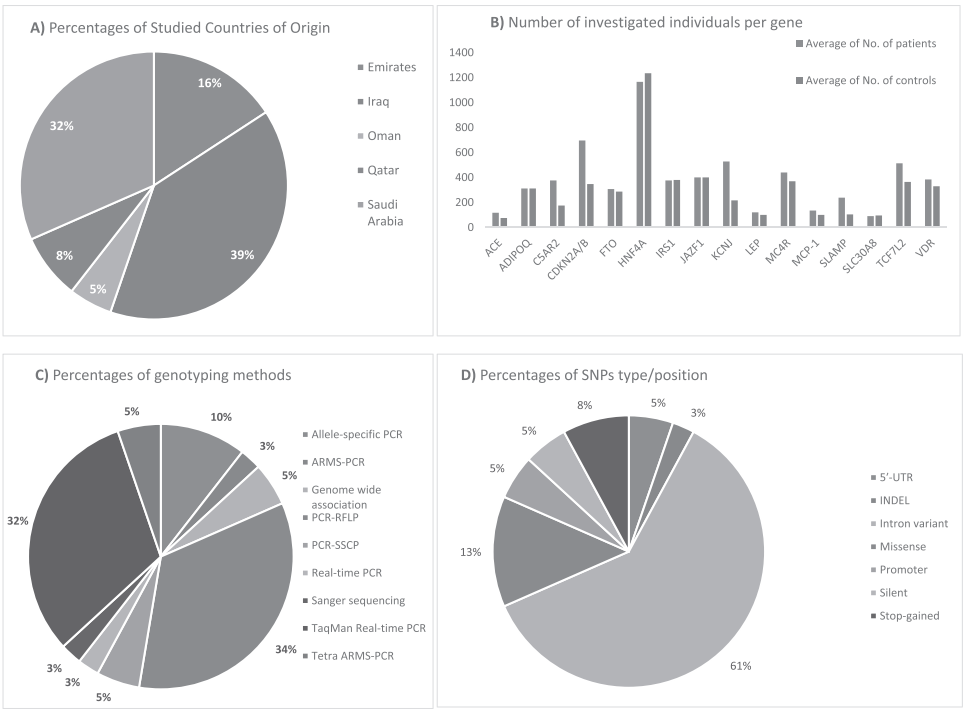

Fig. 2 The main probability measures of the study, in which studied countries of origin, the studied individuals (patients and controls) per gene, genotyping protocols, and SNP description are shown in **A, B**, **C**, and **D**, branches, respectively

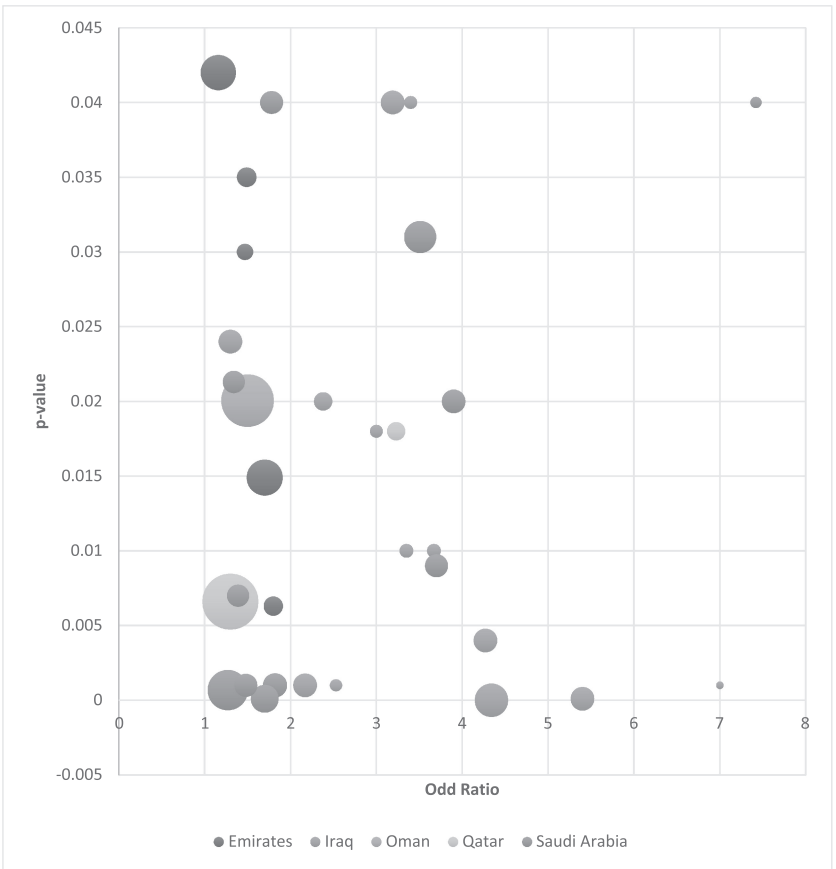

Fig. 3 Bubble chart of odd ratios and *p*-value for T2DM in Arab Gulf Population

suggest a stronger association between the genetic variant and the disease outcome. It is important to note that the studies with ORs between 1 and 2 also tend to have higher sample sizes compared to those with higher odd ratios. Specifically, the studies with the highest ORs (between 7 and 8) have the lowest reported sample sizes. This suggests that the associations observed in these studies may be more prone to bias or chance findings due to smaller sample sizes. In contrast, the associations observed in the studies with odd ratios between 1 and 2 may be more reliable due to their larger sample sizes, despite the range of p-values reported. Therefore, while the ORs provide some indication of the strength of the association between the genetic variant and disease, it is also important to consider the sample sizes of the studies when interpreting the results.

The data of this study indicated that the *TCF7L2* gene represents the most pathogenic gene in terms of the number of identified T2DM-related SNPs. Within this gene, rs7903146, rs12255372, rs4506565, and rs10885409 showed the highest level of pathogenicity in terms of their association with the developments of T2DM in the majority of Arab Gulf countries, whereas the other pathogenic genes did not exhibit such accumulated association with the onset of T2DM. The *TCF7L2* SNPs showed variable degrees of significant associations with T2DM in Saudi, Emirati, Iraqi, and Qatari populations [34–36, 38–41, 51, 52]. However, all the observed associations are located in intron sequences and no other signification association was identified within the sequences of the *TCF7L2* gene. In addition to the findings of the intron SNPs of *TCF7L2* gene, one intronic SNP of the *HNF4A* gene (rs4812829) has given noticeable outcomes in the genotype-phenotype association in this region. Due to the highest number of incorporated populations, it can be stated that this SNP is the most extensively investigated in the Arab Gulf. The polymorphism of HNF4:rs4812829 SNP was found to be significant in Saudi patients with T2DM yielding a considerable risk for patients with T2DM [26]. HNF4 is also known to be involved in insulin-signaling pathways [58]. This suggestion is supported by the generated Panther pathways, which may explain a possible role for this pathogenic SNP in altering and affecting this scheduled role of metabolism. Several other examples showed the high availability of intronic variation in relation to T2DM in Arab Gulf countries. One of these examples is represented in the *MCP-1* gene, which encodes for monocyte chemoattractant protein-1 gene that plays a principal role in the inflammatory process [59, 60]. Within the *MCP-1* gene, the intronic SNP rs1024611 was significantly associated with increased susceptibility to diabetic foot ulcers in Iraqi T2DM Patients [45]. The *FTO* gene polymorphism of the intron rs9939609 SNP showed a significant association with BMI and HDL-C levels in obese diabetic Iraqi males but did not affect other tested biochemical parameters [30]. The polymorphisms of this SNP and rs17817449 of the *FTO* gene may participate in the development of insulin resistance and hence the occurrence of T2DM in obese patients in Iraqi people [31]. On the contrary, non-significant results were detected between the rs9939609 SNP and T2DM in the Western Saudi population and Emirates [33, 39]. Furthermore, another study conducted on Saudi subjects indicated the absence of any significant association between this SNP and T2DM [32]. Based on the GWAS data, the intronic *MC4R*:rs6567160 SNP also showed a significant association with T2DM in the Emirati population [34]. Two intronic variants of the *CDKN2A/B* gene were also found to exhibit significant associations with T2DM in Arab Gulf countries. *CDKN2A/B* gene rs10811661 SNP was implicated in T2DM pathogenesis, whereas the other intronic variant (rs2383208 SNP) did not impact the disease in the Iraqi population [42]. Further confirmation of the role of the intron rs10811661 SNP in the susceptibility to T2DM was also suggested in a wider spectrum of samples in the Omani subjects [43]. On the other hand, other pathogenic SNPs have been found to exhibit a different

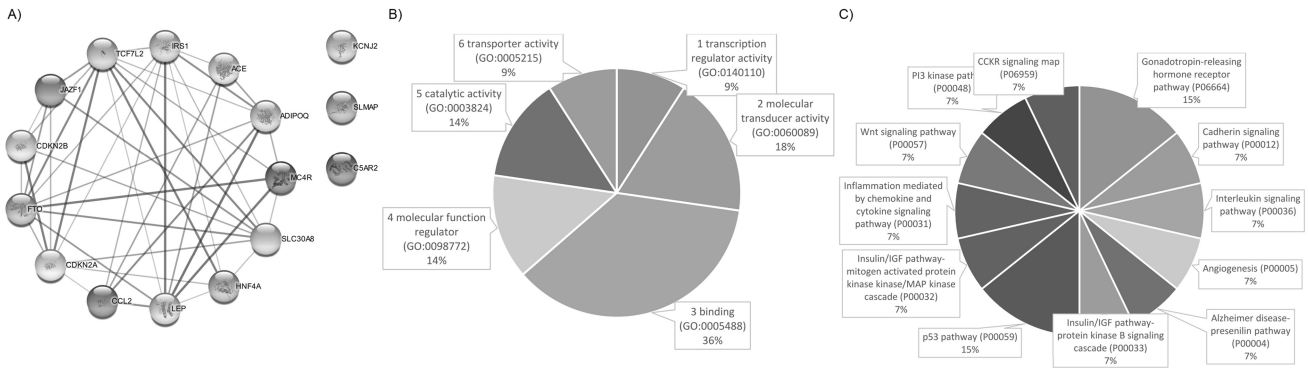

Fig. 4 Bioinformatics analyses of the T2DM-related genes captured in this study. **A** Predicted protein-protein interaction of the captured genes. **B** Predicted molecular functions ratio among the encoded products. **C** Predicted the cellular pathways in which the captured T2DM-related genes are involved

mechanism in relation to T2DM. This can be exemplified in the significant relationship between *C5AR2*; rs149572881, which induced a missense effect of p.233Pro>Leu on the protein, with T2DM in the Saudi subjects [20]. Due to this amino acid substitution, a direct effect of this SNP on the encoded G-protein coupled receptor 1 would be expected [61]. Another example of the effect of the non-synonymous SNP on the development of T2DM in the Arab Gulf is found in the *IRS1* gene, or insulin receptor substrate-1 gene that is implicated in the risk of T2DM [62, 63]. Mutations in this gene have been linked to T2DM and insulin resistance [64, 65]. The genetic polymorphisms of two missense SNPs of *IRS*-1 gene (rs1801278 and rs2943641) have been shown to significantly impair IRS1 function and its subsequent association with T2DM in Saudi subjects [49], whereas *KCNJ2* gene followed another mechanism of association with T2DM by directly truncating its encoded protein by one stop-gained (rs5219) SNP. This SNP showed a significant association with the susceptibility of T2DM in the Iraqi subjects [46], which has also been confirmed by two large-scale investigations performed in Omani and Saudi subjects. Both studies indicated the significant association of this SNP with the risk of T2DM [43, 47]. However, no direct association between rs5219 and T2DM was detected in Emirati subjects [39].

Among all the identified T2DM-related SNP, only one INDEL SNP was found in the *ACE* gene. Recent data indicated an evident association between genetic polymorphism of *ACE*:rs1799752 and T2DM in Iraqi subjects [21, 66]. In agreement with the predicted network of T2DM-related genes, many disorders, including renal disease, stroke, and Alzheimer's disease, have been linked to the polymorphism of the *ACE* gene [67]. *ADIPOQ* gene exhibited two T2DM SNPs, in which one SNP is located in the coding sequences with silent effects and two SNPs located in the promoter sequences. The distribution of *ADIPOQ*:rs266729 SNP in T2DM patients was significantly associated with T2DM in Iraqi subjects [25]. Within the promoter region of the *ADIPOQ* gene, the polymorphism of the rs17300539 SNP was also implicated in the development of T2DM, which caused variable metabolic changes in diabetic Iraqi patients [24]. In addition to intron variation, the *LEP* gene also exerted its effect by a 5′-UTR-SNP (rs11761556). This data is in line with its reported association with insulin resistance and the emergence of T2DM [68, 69]. Another example of the effect of the UTR-SNP on T2DM in the Arab Gulf is found in the *SLMAP* gene. *SLMAP*:rs17058639 SNP has also been suggested to act as a risk factor for the susceptibility to diabetic retinopathy in Qatari patients with T2DM [48]. On the other hand, the *VDR* gene, which affects a range of metabolic pathways [70], showed variable types of pathogenic SNPs associated with the T2DM in the Arab Gulf countries that ranged from intronic (rs1544410 and rs1544410), to silent (rs731236), and missense (rs2228570).

Whatever the mechanism through which each identified SNP exerts its significant association with the onset of T2DM in the Arab Gulf, this meta-analysis has highlighted the genetic loci candidates associated with T2DM in the Arab Gulf population and assessed their potential for early diagnosis of the disease. It shed light on the extent of the association between genetic loci candidates and T2DM in the Arab Gulf population.

Conclusions

The study identified 27 pathogenic SNPs in 16 genes that were located in variable positions in the human genome in the Arab Gulf countries. The *HNF4A* gene was found to exhibit the most common association with T2DM based on the large sample sizes included. The *TCF7L2* gene was found to be the most extensively screened gene in Arab Gulf, with four intron SNPs exhibiting significant pathogenic associations with T2DM in four countries using variable genotyping techniques. The conducted meta-analyses suggest a moderate association between the captured genes and T2DM. However, it is important to note that the studies with higher ORs tend to have smaller sample sizes, which may make their results more prone to bias or chance findings. In contrast, the associations observed in studies with ORs between 1 and 2 may be more reliable due to their larger sample sizes, despite the range of p-values reported. The *in silico* analyses of the identified T2DM-related genes indicated the presence of variable intensities of network interaction among the 13 genes, which suggests the presence of numerous levels of collaboration among them. The results suggest that intronic variation may play a significant role in the development of T2DM in Arab Gulf countries. The variability of genes and SNPs associated with T2DM among different Arab Gulf populations emphasizes the need for further research and personalized approaches to manage and prevent T2DM. The study of genetic variants holds promise for improving the early detection of T2DM in the Arab Gulf population, ultimately leading to better health outcomes and quality of life for those affected by this chronic dysfunction.

Author contribution K. N. J. M. designed the study and conducted the literature search. M. R. conducted the data extraction and analyzed the statistical data. M. B. S. A. conducted the in silico analyses and wrote the manuscript. All the authors revised the subsequent drafts for important intellectual content, read, and approved the final version of the manuscript. Both K. N. J. M. and M. R. contributed equally to this work.

Data Availability The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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