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META-ANALYSIS

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A meta-analysis and review on genetic mapping of type 2 diabetes mellitus in Iraq

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Abstract

Background The prevalence of type 2 diabetes mellitus (T2DM) has been increasing rapidly in Iraq over the past few decades. Identifying the most significant factors contributing to the development of T2DM is crucial to reducing its prevalence in this region. Genetics and epigenetics have been shown to play a role in the initiation of T2DM, making it essential to study the genetic variations of diabetic patients to identify common biomarkers associated with this disorder in Iraq.

Methods We conducted a systematic review and meta-analysis of published data to identify potential pathological indicators associated with T2DM in Iraq. We searched various databases and included studies that reported the association between genetic biomarkers and T2DM in Iraqi patients. We then analyzed the data using a random-effects model to estimate the overall effect size and identify the most common biomarkers associated with the risk of T2DM.

Results We identified 31 explored genes in 41 studies that exhibited the most common biomarkers with a strong association with the risk of T2DM in Iraq. Our exploration embraced genomic, demographic, and sensitivity analyses, enriching insights.

Conclusions Our study provides valuable insight into the genetic SNPs associated with T2DM in Iraq and offers a foundation for future research in this area. The identified SNPs can help in the development of personalized treatment options, leading to better disease management and improved patient outcomes. The study also highlights the need for further investigation into potential genetic SNPs and factors that may contribute to the development of T2DM in Iraq. While our study is limited by the sample sizes of some of the included studies, it provides a starting point for researchers seeking to identify common diagnostic markers for T2DM in Iraq.

Keywords Bioindicators, Bioinformatics, Diabetes risk factors, Genetic mapping, Type 2 Diabetes Mellitus (T2DM)

Introduction

Background

Diabetes is a chronic condition that affects a sizable fraction of the global population. Given its alarming prevalence, contemporary medicine has made major research efforts. Particularly, type 2 diabetes mellitus (T2DM) has been shown to be a complex and multifaceted condition, necessitating further research to identify the most efficient countermeasures. Iraq is one of the Middle Eastern nations with the highest prevalence of diabetes, making it the nation's top public health priority [1].

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Despite its high prevalence, the healthcare infrastructure in Iraq has been severely damaged by the aftermath of the wars in the last four decades, compounded by ongoing economic sanctions that continue to constrain the nation's ability to provide suitable budgets for healthcare services [2]. As a result, many diabetes patients and those with diabetes-related symptoms cannot access proper treatment, as there is no effective insurance system in place. In addition, the effect of culture upon diet results in many Iraqi people consuming excessive calories, particularly carbohydrate- and sugar-rich foods, which has contributed to an increased risk of T2DM in the Iraqi population [3]. Furthermore, there is evidence that the Iraqi population is unique in having greater-than-average resistance to insulin, which is crucial to understanding the risk factors that pertain to this population [4, 5]. Despite the common notion that genetics is a key factor in T2DM, there is an absence of consensus as to the extent to which genetics is deemed to be the primary factor [6]. It has been suggested that T2DM has 80% heritability, while other reports indicated that the effect of genetic factors could not get beyond 25% [7–9].

The risk factors for the incidence of T2DM can be categorized as pathophysiological attributes that are identified as dysfunctional genes that are associated with the progression of this disease by the means of their variations [10]. Investigating these candidate genetic variants can largely determine the pathways and mechanisms responsible for causing T2DM. Studies on diabetes candidate genes have discovered increasing numbers of genes linked to the risk of T2DM by their causative variations [11]. With the aid of genome-wide association studies (GWAS), it has been found that the number of these T2DM-related genetic variations is steadily increasing [12]. Despite the lack of comprehensive data for the early diagnosis of T2DM in the Iraqi population, a systematic review is provided to jointly examine and collect information on the association between genetic variations and T2DM in this population to develop a complete strategy to combat the steady expansion of this disease. The objective of the study is to systematically identify the genetics and map the local genes associated with T2DM in the Iraqi population, to aid the Iraqi government in making necessary provisions and to aid healthcare practitioners in providing their patients with care that is as effective as possible.

Overall, understanding the genetic factors that contribute to the risk of T2DM in the Iraqi population is critical to developing effective strategies for managing this disease. By identifying the specific genes associated with T2DM, healthcare providers and policymakers can develop targeted interventions to prevent and manage the disease in the Iraqi population.

Structure

This study is structured as follows. Sect. "Introduction" provides a brief background on Type 2 Diabetes Mellitus (T2DM) and its prevalence in Iraq. This section also discusses the importance of genetic mapping in understanding the genetic basis of T2DM and its potential for personalized treatment. Sect. "Meta-analysis methodology" describes the methodology used for the meta-review of genetic mapping studies on T2DM in Iraq. This includes the search strategy, study selection criteria, and data extraction process. Sect. "Results and discussion" presents the results of the meta-review, including the identified genetic variants and their associations with T2DM in the Iraqi population. This section also discusses demographic and sensitivy analysis using the collected studies. Sect. "Conclusion" concludes the paper by summarizing the main findings of the meta-review and their implications for personalized treatment of T2DM in Iraq. The section also highlights the importance of continued research in this area and the potential for genetic mapping to contribute to the development of targeted therapies.

Meta-analysis methodology

Study design

This meta-analysis aimed to analyze and review the genetic mapping of T2DM in Iraq. The analysis was conducted using data from previously published studies, and the results were synthesized to provide a comprehensive overview of the genetic loci associated with T2DM in Iraq. Figure 1 illustrates the PRISMA process flowchart used in order to perform this meta-analysis. The first step is to identify the research question associated with this meta-analysis, which is:

1. What are the genetic variants associated with T2DM in the Iraqi population?
2. Which of the identified genetic variants exasperate the effects T2DM?
3. Which of the identified genetic variants exert a significant protection against T2DM?

The next step is to identify the databases and conduct a literature search. But in order to do this, the relevant databases and libraries must be identified. Databases such as PubMed, Scopus, and Web of Science are among the considered set of libraries. The search is performed using relevant keywords and MeSH (Medical Subject Headings) terms related to type 2 diabetes, genetic mapping, and the Iraqi population.

Next step is screening of titles and abstracts, this is done in the eligibility step. Review the titles and abstracts of the

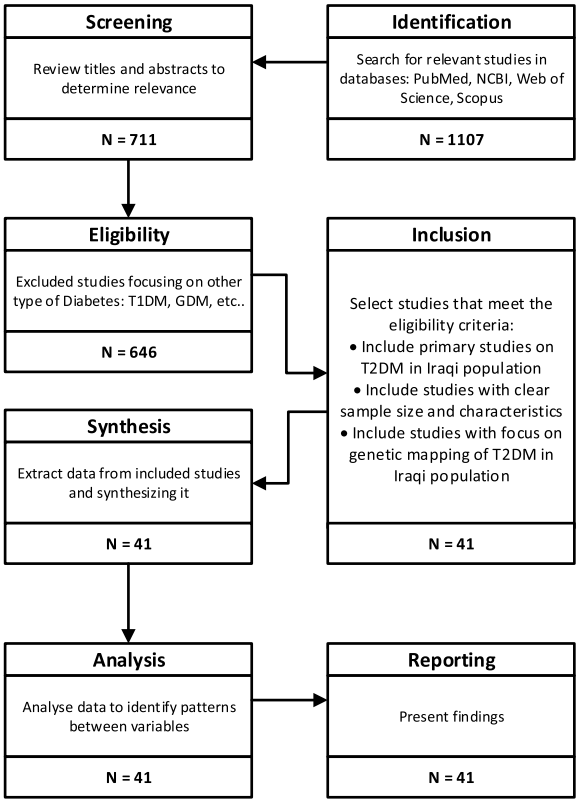

Fig. 1 PRISMA Flowchart depicting the meta-analysis process performed for Genetic Mapping of T2DM in Iraq

identified studies to determine their relevance. Include studies that report genetic variants associated with T2DM in the Iraqi population. The next step is the screening of the full text. Review the full-text of the selected studies to determine their eligibility for inclusion in the meta-analysis.

The next step is to extract the relevant data from the included studies, including the author, year of publication, sample size, demographic information, genetic variants (genes, loci), and statistical measures (p-value, odd-ratio). Once extracted, the data is analyzed the using appropriate statistical methods, to identify the genetic variants associated with T2DM in the Iraqi population. In the end of the process, the results of the report are displayed.

Literature search and extraction

A comprehensive search was conducted to identify relevant studies in electronic databases, including PubMed, NCBI, Web of Science and Scopus. The search strategy was conducted using the following keywords:

$$(\text{Type 2 Diabetes Mellitus OR T2DM}) \text{ AND } (\text{Genetic Mapping}) \text{ AND (Iraq)}$$

With the aid of this keyword, 1107 studies were identified, and through a screening process, they were reduced down to 711 studies. Inclusion criteria were studies conducted on the Iraqi population, with genetic loci information on T2DM. Exclusion criteria were studies not conducted in Iraq, studies without genetic loci information, and studies not related to T2DM. Additionally, studies that did not have the statistical data required, such as confidence intervals and odd ratios, as well as population and control sizes, were also excluded. This is an important factor, as without the odd-ratio and the weight, it is not possible to perform a sensitivity analysis. Through this inclusion and exclusion process, the total number of studies was reduced to only 41 studes.

Data extraction

Data were extracted from the included studies, including sample size, number of cases and controls, genetic loci information, and other relevant variables. The genetic loci information from new data 7893 patients and 5064 control participants was obtained from studies conducted all over Iraq. The data were collected and stored in a database, and duplicates were removed. The data were then checked for accuracy, and any discrepancies were resolved by discussion among the research team.

Data synthesis and analysis

The data were analyzed using a random-effects model to estimate the overall effect size and the 95% confidence interval (CI) of each genetic locus. The random-effects model takes into account the variability between studies, and provides a more conservative estimate of the effect size. Subgroup analyses were conducted to explore the potential sources of heterogeneity. The subgroup analyses were based on the ethnicity of the study participants, the sample size, and the quality of the studies.remove it.

Sensitivity analysis

Sensitivity analysis was performed through the Forest plot analysis, in which the odd ratios as well as the population size, confidence inervals and weights were used in order to get a better understanding of the relationship between the studies and the presented results. Forst plot is a key illustrations that allows for the deeper understanding between the results of each study, and how they relate to one another.

Statistical software

The statistical analysis was conducted using the R software (version 4.2.2) with the meta package. The meta package provides functions for conducting meta-analysis, including data extraction, data analysis, and data visualization. The R software is a widely used statistical software for conducting meta-analyses and other statistical analyses. Additional tools such as OriginPro were used to aid in data visualization tasks and create clearer diagrams and charts.

Results and discussion

Based on the investigation of the literature in Iraqi population, the analyses have been separated into three main categories. The first analysis focuses the genetic variats that showed to have been significant in risk increase in T2DM. The second analysis focuses on the dempgraphic effect and its various groups and how each group could be interconnected. Finally, the third analysis uses the information from the studies and performs a sensitivity analysis based on their population sample size and their Odd-ratio.

Genomic analysis

Several genes associated with T2DM and related complications have been identified in the Iraqi population. The patterns of their associations with T2DM were extensively studied in Iraqi community and listed in Table 1 and further illustrated in Fig. 2.

The Vitamin D receptor gene, *VDR*, displayed a significantly larger number of patients (1677) compared to controls (817), indicating a potential role in T2DM pathogenesis. Vitamin D's metabolic functions may contribute to this association. *ADIPOQ*, which encodes the adiponectin protein, showcased a notable difference in patient (1470) and control (735) counts. Adiponectin's regulatory role in glucose metabolism underscores its importance in T2DM risk.

The *FTO* gene, linked to obesity, displayed substantial patient (1600) and control (800) counts. Obesity's intricate relationship with T2DM suggests *FTO*'s potential involvement in the disease's onset. *CDKN2A/B*: This gene pair, associated with cell cycle regulation, exhibited a significant difference in patient (800) and control (400) counts. Its role in pancreatic β-cell function and cell cycle control could contribute to T2DM susceptibility.

The analysis highlights genes with notable differences in patient and control counts, suggesting their potential involvement in T2DM risk within the Iraqi population. These findings align with existing knowledge of metabolic and regulatory processes implicated in T2DM development. In order to further elaborate on the effect the genes have, each gene is explained with their associated reference.

ACE (gene ID: 1636): *This* gene was also known as *ACE1, CD143, DCP,* and *DCP1*. *ACE* gene positioned in chromosome 17 and encodes for angiotensin I converting enzyme. This enzyme was involved in numerous metabolic pathways, including the control of neuronal plasticity, electrolyte balance, and blood pressure [13]. Some of the Iraqi population exhibit polymorphic *ACE* I/D, which was associated with T2DM; furthermore, the *AGT M235T* allele was absent in the same population (Iraqi population) [14]. According to Dhumad [15], the DD genotype and D allele of the *ACE* I/D polymorphism are risks factor for T2DM. Indeed, there was an association between the presence of the D allele of this polymorphism and the development of *CAN* in patients with T2DM [15].

ADIPOQ: One of the key adipocyte secretory proteins most often identified in human plasma is adiponectin, which plays important functions in regulating energy balance and glucose tolerance as well as insulin sensitivity in muscle and the liver. The *ADIPOQ* gene, which produces adiponectin, is found on human chromosome 3q27, where three exons that span 17 kb have been identified as a susceptibility locus for metabolic syndrome and T2DM. In a Chinese population, the *ADIPOQ* genetic polymorphisms were linked to T2DM [16]. The findings of the study conducted by Al-saadi (2016), indicates an association between T2DM and a G276T polymorphism in *ADIPOQ*, which codes for adiponectin [17]. This conclusion arose from an analysis of the genotype and allele distribution of *ADIPOQ* rs2241766 gene in T2DM patients [18]. In addition, Algenabi (2021), identified polymorphisms in the promoter region of rs17300539 as contributing to the initiation of T2DM. Metabolic changes in diabetic patients are attributed to this polymorphism [19].

Compared to controls, there was a greater distribution of T45G polymorphisms of in *ADIPOQ* in T2DM patients (mean ± standard error control: 0.160 ± 0.07, T2DM patients 0.515 ± 0.06) [20]. It is considered that in the Al-Najaf Governorate of Iraq, an adiponectin receptor 2 gene SNP is implicated in causing T2DM with Cardiovascular Disease (CVD). The risk of developing of T2DM with CVD is elevated in an individuals with the homozygous genotype (TT) and heterozygous (AT) genotype of rs1106197. Furthermore, there is an association between increased risk of develop T2DM with CVD with the frequency of T allele of rs11061971. Ismail (2016), state that R2 adiponectin receptors are implicated in metabolizing TG and VLDL cholesterol [21]. The polymorphism rs266729 of the adiponectin gene, which is

Table 1 Identified genes that have an impact on T2DM among the Iraqi population

Gene	SNP	Type/position of SNP	No. of patients	No. of controls	Genotype Method	P-Value	OR	City	References	Complications
GSTM1			90	30	PCR-ARMS	0.055	3.06	Baghdad	Mahmood et al. (2015)	CAD
ADIPOQ	rs266729	5′-UTR	270	135	PCR–RFLP	0.001	2.45	Najaf	Ahmed Naseer et al.2015)	No Complications
TGF-β1	rs1800469	–	50	20	PCR-ARMS	0.01	5.23	Baghdad	I. A. Hussein (2016)	No Complications
ADIPOQ	rs1501299	Intron variant	100	50	PCR–RFLP	0.05	0.684	Baghdad	Al-saadi (2016)	No Complications
ADIPOR2	rs11061971	–	336	133	PCR–RFLP	0.049	1.28	Najaf	Ismail et al. (2016)	CVD
FTO	rs9939609	Intron variant	800	400	PCR–RFLP	0.005	1.58	Najaf	Younus et al. (2017)	No Complications
VCAM-1	rs3783605	–	129	61	PCR-SSP	0.007	1.64	Baghdad	Salman et al. (2017)	No Complications
IL-10	rs1800872	–	100	30	PCR–RFLP	0.05	1.5	Basra	Hamid and Shani (2018)	No Complications
ADIPOQ	rs2241766	Missense	800	400	PCR–RFLP	0.002	1.7	Najaf	Hussain et al. (2018)	No Complications
IL-6	rs1800795	–	100	50	PCR–RFLP	0.03	2.17	Baghdad	Shehab et al. (2018)	No Complications
PPARG	rs3856806	–	100	50	PCR-Taqman	0.01	1.272	Baghdad	Abd Al-Razzaq et al. (2018)	No Complications
ELMO1	rs741301	–	73	37	PCR-ARMS	0.0042	4.23	Kerbala	Mohammed et al. (2019)	DN
MCP-1	rs1024611	–	235	135	PCR-ARMS	0.002	2.8	Kerbala	Obied et al. (2019)	DFU
TCF7L2	rs7908486	–	130	60	PCR–RFLP	0.035	1.301	Baghdad	Ahmed et al. (2019)	No Complications
MIR196A2	rs11614913	–	60	30	PCR–RFLP	0.0001	0.22	Najaf	Jamee et al. (2019)	No Complications
KCNJ11	rs5219	–	60	20	PCR–RFLP	0.0014	7	Baghdad	Muftin et al. (2019)	No Complications
TGF-β1	rs1800471	–	117	52	PCR–RFLP	0	1.89	Thi-Qar	Nuhiar et al. (2019)	T1DM
LDLR	A370T	–	180	60	PCR–RFLP	0.001	1.88457	Kerbala	Hassan Abo Almaali (2019)	No Complications
AHSG	rs4918	–	200	100	RT-PCR	0.001	0.4	Kerbala	H. S. M. Ali (2019)	No Complications
VDR	rs10735810	–	77	17	PCR-ARMS	0.005	0.211	Najaf	Najjar et al. (2020)	DN
TCF7L2	rs7903146	–	212	106	PCR-ARMS	0.014	1.65	Erbil	Mustafa et al. (2020)	No Complications
PD-1	rs36084323	–	90	45	PCR–RFLP	0.05	0.18	Baghdad	A. R. Rasheed et al. (2020)	No Complications
ACE	-	–	242	100	PCR–RFLP	0.005	1	Baghdad	Dhumad et al. (2020)	No Complications
LEP	rs7799039	–	112	50	PCR–RFLP	0.0001	1.78	Erbil	G. H. Abdullah (2020)	No Complications
FTO	rs1588413	5′-UTR	800	400	PCR–RFLP	0.001	4.61	Najaf	A. Algenabi et al. (2021)	Obesity
VDR	rs2228570	Missense	800	400	PCR–RFLP	0	4.3	Najaf	Ahmed N Kaftan et al. (2021)	No Complications
KCNQ1	rs2237892	–	600	300	PCR–RFLP	0.001	2.79	Najaf	Al Hussieny et al. (2021)	No Complications
SOST	rs865429	–	300	150	PCR–RFLP	0.0001	0.4444	Najaf	R. A. M. Ali et al. (2021)	CHD
VDR	rs1544410	Intron variant	800	400	PCR–RFLP	0	2.75	Najaf	Al-Kashwan et al. (2021)	No Complications
LEP	rs12706832	–	220	100	PCR-SSCP	0.006	1.75	Kerbala	Musafer et al. (2021)	No Complications
IL-23	rs1884444	–	150	75	PCR-ARMS	0.001	4.2	Baghdad	S Al-Badri et al. (2022)	No Complications
ADIPOQ	rs2241766	Missense	300	150	PCR–RFLP	0.002	1.918	Diwaniyah	Abbas et al. (2022)	No Complications
CDKN2A/B	rs10811661	Exon variant	800	400	PCR–RFLP	0.0001	1.918	Najaf	Fadheel et al. (2022)	No Complications
APOE	rs429358	–	149	73	Conventional-PCR	0.037	1	Baghdad	Hameed et al. (2023)	CVD
IL-17A	rs2275913	–	150	75	PCR-ARMS	0.001	0.29	Kut	Ali Saad Kadhim (2023)	Oral fungi

Table 1 (continued)

Gene	SNP	Type/position of SNP	No. of patients	No. of controls	Genotype Method	P-Value	OR	City	References	Complications
GSTP1	rs1138272	Exon variant	90	30	PCR-ARMS	0.019	1.65	Babylon	Neama et al., (2023)	No Complications
CNDP1	rs2887		100	50	PCR-HRM	0.001	2.77	Baghdad	Shaheed and Ali (2023)	No Complications
PON1	rs705379		100	40	PCR–RFLP	0.0001	5.7	Babylon	AbdAli et al. (2023)	No Complications
WFS1	rs734312	–	200	100	RT-PCR	0.0001	0.86	Diwaniyah	A. J. Hussein et al. (2023)	No Complications
TNF-α	rs1800629	–	100	50	RT-PCR	0.0001	1.52	Diyala	Alaa N. Lateef (2023)	No Complications
PPARG	rs1801282	–	200	100	Sanger-PCR	0.0045	3.96	Erbil	Baqer et al. (2023)	No Complications

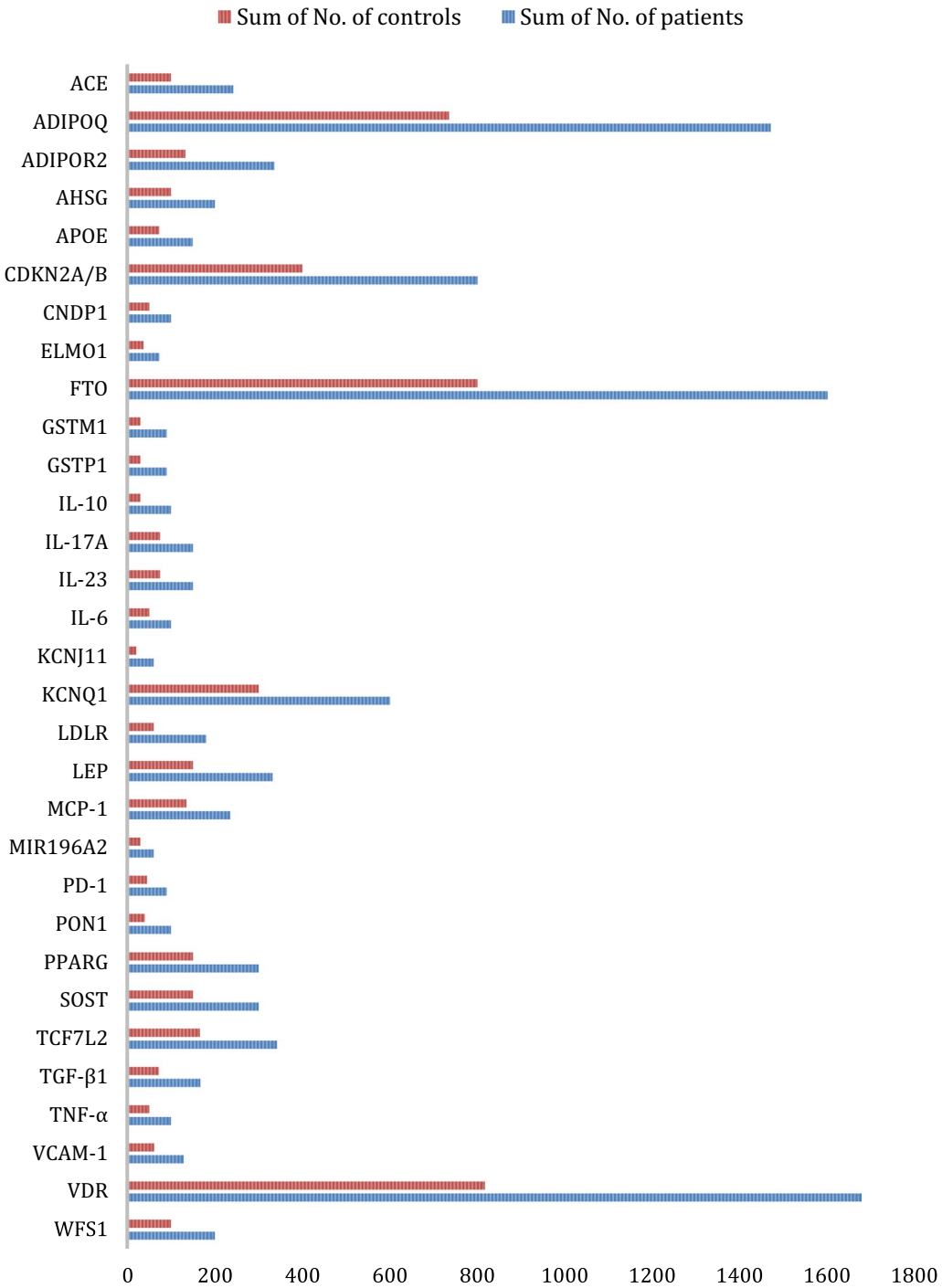

Fig. 2 Genes and their associated population size and control size

also implicated in causing T2DM, might affect levels of HDL and insulin, thereby contributing to CVD and metabolic syndrome [22]. By influencing the concentration of serum lipids and promoting insulin resistance, the presence of the rs2241766T > G SNP of the adiponectin gene is a T2DM risk factor for Iraqi individuals [23].

AHSG: The liver releases fetuin-A also referred to as a-Heremans-Schmid glycoprotein, which binds to the insulin receptor tyrosine kinase in peripheral tissues and inhibits the insulin-induced intracellular signal cascade, leading to peripheral insulin resistance. Human linkage studies of traits including metabolic syndrome

and T2DM have located the locus (3q27) where the gene encoding fetuin-A (*AHSG*) is located. In a recent study, we also discovered a link between plasma fetuin-A levels and the risk of T2DM in a sizable sample of older persons living in the community who took part in the Cardiovascular Health Study (CHS) and were monitored for a median of 11 years [24]. Ali (2019) found a significant difference in the GC and GG genotypes of healthy individuals and T2DM patients. For those with the GC phenotype, the risk of T2DM was double that of those individuals with the GG phenotype (respective OR: 2.27, χ^2 8.11 vs 0.4, χ^2 9.74 [25]

APOE: The gene's product is a significant apoprotein within chylomicrons. It binds to specific receptors in the liver and peripheral cells, playing a vital role in the regular breakdown of lipoprotein components rich in triglycerides. This gene is located on chromosome 19 alongside related apolipoprotein C1 and C2 genes. Mutations in this gene lead to conditions like familial dysbetalipoproteinemia or type III hyperlipoproteinemia (HLP III), characterized by elevated plasma cholesterol and triglycerides due to impaired elimination of remnants from chylomicrons and VLDL [26]. Genetic variations in the *ApoE* gene, particularly in SNPs rs429358 and rs7412, could potentially act as predisposing factors for T2DM and CVD in Iraqi patients [27].

CDKN2A/B: This gene produces many transcript variants, each of which has a unique first exon. Two of the at least three alternatively spliced variants found encode proteins with structurally similar isoforms that are known to act as *CDK4* kinase inhibitors. *CDKN2* gene is a recognized key tumor suppressor gene that is commonly altered or deleted in some tumor types [28]. Whilst the rs2383208 SNP did not impact the disease among the Iraqi population, there is evidence that the rs10811661 SNP affects insulin levels in T2DM patients [29].

CNDP1: This gene encodes a member of the M20 metalloprotease family. The protein produced by this gene has exclusive expression in the brain and takes the form of a homodimeric dipeptidase, identified as human carnosinase. A trinucleotide (CTG) repeat length polymorphism is present in the coding region of this gene [30]. The variation (rs2887) within the *CNDP1* gene indirectly contributes to the emergence of CVD in individuals with T2DM in Iraq. This variation leads to elevated serum levels of carnosinease-1, subsequently enhancing the breakdown of carnosine, thus potentially influencing CVD development [31].

ELMO1: A novel and promising candidate gene called *ELMO1* (Engulfment and Cell Motility 1), which is found on chromosome 7p14.2–14.1, is responsible for cell motility and the phagocytosis of apoptotic cells [32]. Mohammed (2019), report that individuals in Kerbala/Iraqi province with polymorphisms at the rs741301 region of the *ELMO1* gene are vulnerable to the T2DM complication of DN [33].

FTO: It was first discovered as a gene involved in programmed cell death. Three investigations conducted in 2007 showed a connection between body mass and differences in *FTO*. There are many polymorphisms known. In comparison to those without a risk allele, the 16% of people who are homozygous for the risk allele SNP rs9939609 weigh roughly 3 kg heavier and have a 1.67-fold greater risk of obesity. This connection may be noticed in people aged 7 and older and implies a particular rise in fat mass [34]. Al-Tu'ma & Obed (2018), found a significant association between the *FTO* gene polymorphism, rs9939609, and levels of HDL cholesterol in obese, male Iraqi T2DM patients [35]; however, no association between this polymorphism and other biochemical parameters was detected. Younus (2017), report that rs9939609 and rs17817449 polymorphisms of the *FTO* gene contribute to insulin resistance, increasing the prevalence of T2DM in obese patients [36]. The work by Algenabi (2021), supports those earlier findings, noting that in obese patients, rs17817449 and rs1588413 polymorphisms are effective predictive markers of developing T2DM [37]. Thus, the risk of developing of T2DM might be elevated by variations in the G276T polymorphism in the adiponectin gene.

GST (M1, P1): Glutathione S-transferase (*GST*) family proteins are enzymes that detoxify a variety of dangerous chemicals, such as reactive oxygen species (ROS) or xenobionts [38]. According to the current findings, T2DM patients with the *GSTT1* positive genotype are afforded some protection against the risk of CAD [39]. Mahmood (2015), determined the *GSTM1* positive genotype to be a CVD risk factor for patients with T2DM [40]. We found the prevalence of the GSTP1 heterozygous mutant allele Ile/Val to be lower in controls than in patients with T2DM (30% vs 40%; $P=0.01$). Furthermore, the homozygous mutant of *GSTP1* allele Val/Val, was not identified in any of the controls, but was found in 3.33% of T2DM patients ($P=0.001$). After the onset of T2DM, *GSTP1* genotypes do not influence blood lipids. Agarose gel electrophoresis was used to determine genotypes, which produces bands in the gel [41].

IL-17: The encoded protein for the *IL-17* gene, which belongs to the five-member *IL-17* receptor family (*IL-17RA-E*), is a pro-inflammatory cytokine generated by activated T cells [42]. It is considered to be an important risk factor for the onset of T2DM. Furthermore, elevated HOMA-IR values correspond to hyperglycemia, so is another T2DM risk factor [43].

IL-10: Human *IL-10* is produced by a gene on chromosome one (1q31-32). Additionally, three biallelic polymorphisms for *IL-10* have been discovered at locations -1087, -824, and -597 from the transcription start site23 [44]. The *IL-10* (-592A/C) gene polymorphism was identified by Hamid & Shani as being a contributor to developing T2DM [45].

IL-23: A member of the *IL-12* family, *IL-23* has two components, p40 and p19, and is generated by dendritic cells, monocytes, and macrophages. Th17 effector cells can grow and remain active as a result of *IL-23* attaching to its heterodimeric receptor. The receptor may be seen on the surface of macrophages, monocytes, dendritic cells, and lymphocytes. While the p19 subunit of *IL-23* has a distinct and strong affinity for *IL-23R*, the p40 subunit of *IL-23* is shared with *IL-12*. *IL-23R* is involved in the initiation and maintenance of *IL-23/IL-17* signal transduction; changes to the signaling pathway may result in the deregulation of the inflammatory response [46]. Al-Badri (2022), determine that GT and TT of SNP (rs1884444G/T) promoted the risk of T2DM and oral fungal infection [47].

IL-4, IL-6: *IL-4* gene produces a pleiotropic cytokine by T cells that have been stimulated. The interleukin 4 receptor is a ligand for this cytokine. The interleukin 4 receptor binds to *IL13* as well, which may help explain why these two cytokines have many similar roles [48]. *IL-6* gene produces a cytokine that aids in B cell development and inflammation. Additionally, it has been demonstrated that the encoded protein functions as an endogenous pyrogen that can cause fever in persons with autoimmune disorders or infections. The interleukin 6 receptor alpha is the place where the protein is largely generated, where it is released into the serum and triggers a transcriptional inflammatory response. Numerous inflammation-related disease conditions, such as susceptibility to diabetes mellitus and systemic juvenile rheumatoid arthritis, are linked to the activity of this gene. Infections with viruses, such as COVID-19 [49]. According to the works by Shehab and Khdaer there is an association between heterozygous GC genotypes and T2DM. Also, a robust relationship was identified between the levels of *IL-6* and T2DM and IR groups. Specifically, the incidence of T2DM and IR are elevated with the CC variation of *IL-6* (-174) 9 [50, 51].

KCNJ11: The potassium channel gene *KCNJ11*, which belongs to that family, is found at 11p15.1 and lacks an intron. An inward-rectifier potassium ion channel is encoded by this gene (Kir6.2). The KATP channel is made up of the Kir6.2 proteins and the high-affinity sulfonylurea receptor 1 (SUR1). The *ABCC8* gene, which is adjacent to the *KCNJ11* gene, encodes SUR1. The Kir6.2 proteins is a 390 amino acid protein having intracellular N- and C-terminals and two transmembrane domains (M1 and M2). The KATP channel in the plasma membrane of pancreatic beta cells is structurally made up of four high-affinity SUR1 subunits that envelope the pore, which is formed by Kir6.2 tetramers. Via glucose metabolism, that channel regulates insulin secretion and synthesis [52]. Although an association has been determined between the E23K; rs5219 SNP and T2DM, more research is need to establish the strength of that association [53].

KCNQ1: The slow delayed rectifier current (IKs) that occurs after the repolarization of the cardiac action potential is caused by the *KCNQ1* gene, which encodes the α-subunit of the voltage-gated potassium channel Kv7.1. Pathogenic missense variations frequently show a dominant-negative impact that can be attributed to interference with the wild-type (WT) subunits translated from the non-affected allele because the *KCNQ1*-encoded -subunits tetramerize during Kv7.1 channel construction [54]. From a sample of the Iraqi population, Al Hussieny determined that rs2237892, and rsl51290 polymorphisms of this gene are T2DM risk factors [55].

LEP: This gene produces a protein that is released into the bloodstream by white adipocytes and is crucial for maintaining the balance of energy. The brain's leptin receptor binds to circulatory leptin, activating the signaling pathways that prevent overeating and encourage energy expenditure. This protein also was associated with the control of immunological and inflammatory responses, hematopoiesis, angiogenesis, reproduction, osteogenesis, and wound healing. It plays several endocrine roles [56]. Consistent with the findings of Musafer (2022), our study found a robust association between rs11761556 and rs12706832 SNPs and T2DM. These SNPs could be used as biomarkers for the early detection of T2DM [57].

LEPR: This gene produces a protein that belongs to a member of the gp130 family of cytokine receptors, which are reported to activate cytosolic STAT proteins to promote gene transcription. This protein is a leptin receptor that regulates fat metabolism and participates in a brand-new hematological pathway necessary for healthy lymphopoiesis. Obesity and pituitary dysfunction have been linked to mutations in this gene [58]. According to Ahmed & Ghali (2017), susceptibility to T2DM is indicated by the presence of the rs1137101 (Q223R) polymorphism in the *LEPR* gene. This could also be exploited as a biomarker for T2DM [59].

LEP 2548 G/A: Unclear evidence links *LEP*/*LEPR* to overweight/obesity and the associated metabolic abnormalities. These outcomes can be the result of unknown gene-environment interactions. But in Iraqis Individuals in Erbil who have elevated serum concentrations of leptin

and carrying the A allele carrier may be at greater risk of developing T2DM [60, 61].

MCP-1: On chromosome 17's q-arm, several cytokine genes are grouped, including *MCP-1*. A subfamily of secreted proteins known as chemokines has a role in both inflammatory and immunoregulatory processes. Based on the configuration of the mature peptide's N-terminal cysteine residues, the superfamily is subdivided into four subfamilies. The CC subfamily, which includes this chemokine, is distinguished by two adjacent cysteine residues. For monocytes and basophils, but not for neutrophils or eosinophils, this cytokine has chemotactic action. It has been linked to the pathophysiology of illnesses including psoriasis, rheumatoid arthritis, and atherosclerosis which are characterized by monocytic infiltrates. It binds to the CCR2 and CCR4 chemokine receptors. The coronavirus 2 infection that causes severe acute respiratory syndrome is linked with increased expression of the encoded protein [62]. A significant relationship was determined between the rs1024611 polymorphism and greater DFU susceptibility in Iraqi T2DM patients. Compared to T2DM patient without DFU, the frequency of AG and GG genotypes was higher in those with DFU [63].

MIR-196A2: MicroRNAs (*miRNAs*) are small (20–24 nt) non-coding RNAs that influence the stability and translation of mRNAs to regulate gene expression in multicellular animals post-transcriptionally [64]. Jameel (2019), study identified the association between the miR-196a2 polymorphism and T2DM [65].

PD-1: negatively controls the immunological response. acts before or inside of the negative regulation of apoptosis, the negative rule of tolerance induction, and the positive regulation of apoptosis. it is situated on the plasma membrane's outer side. is seen in the retina. used to research systemic lupus erythematosus and dilated cardiomyopathy. This gene's human ortholog (s) has been linked to lupus nephritis, hepatitis B, hepatitis C, and various autoimmune diseases [66]. The data from Rasheed (2020), point to the A allele of *PD-1*–538 G/A being a possible risk factor for developing T2DM. Compared to other genotypes of this polymorphism, the GG variant is linked to elevated serum levels of *sPD-1* [67].

PPARG: A nuclear receptor belonging to the peroxisome proliferator-activated receptor (*PPAR*) subfamily is encoded by this gene. *PPAR*-alpha, *PPAR*-delta, and *PPAR*-gamma are the three subtypes of *PPARs* that are recognized. This gene produces the *PPAR*-gamma protein, which controls the development of adipocytes. *PPAR*-gamma has also been connected to the pathophysiology of several illnesses, including cancer, DM, atherosclerosis, and obesity [68].

The results showed that the distribution of genotypes and alleles frequencies at (rs1801282) SNP of *PPARG* gene, as related with CC, CG, and combined CG + CC genotypes, G allele seems to be a protective allele, therefore, the presence of both heterozygous and homozygous mutants may reduce the risk of T2DM (the frequency of CG + GC mutants were 68% in apparently healthy control individuals and 50% in T2DM patients). In contrast, there is a wild CC genotype (50 versus 32% in T2DM and control group, respectively, $X^2 = 6.93$; $P < 0.01$; OR = 1.272) [69].

SOST: Sclerostin is a secreted glycoprotein that shares sequence similarities with the DAN (differential screening-selected gene aberrative in neuroblastoma) family of bone morphogenetic protein (BMP) antagonists and has a C-terminal cysteine knot-like (CTCK) domain. This gene's loss-of-function mutation is linked to the autosomal-recessive condition sclerosteosis, which results in progressive bone overgrowth [70]. Ali (2021), state the risk of CAD is high in T2DM patients who have the T allele and increased plasma concentrations of sclerostin [71].

TNF: A multifunctional proinflammatory cytokine from the tumor necrosis factor (*TNF)* class is encoded by this gene. Mostly macrophages secrete it. It can bind to and work through the TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR receptors. Numerous biological processes, including cell division, proliferation, apoptosis, lipid metabolism, and coagulation, are regulated by this cytokine. *TNF* has been connected to several illnesses, including cancer, autoimmune disorders, insulin resistance, psoriasis, rheumatoid arthritis, ankylosing spondylitis, and TB [72].

Al-Hilali (2015), found insulin resistance in T2DM patients to be significantly greater than controls. The researchers noted a correlation between insulin resistance and the AA genotype with an A allele polymorphism. Whilst our work, supports the earlier findings of the A allele being associated with susceptibility to T2DM, we found the G allele to confer protection against the disease [73]. Mousa (2018), suggests that the A allele of the *TNF-α* gene could contribute to the prevalence and susceptibility Al-Muthanna and Baghdad province's population to T2DM [74, 75].

TGF-β1: (transforming growth factor-beta) superfamily of proteins' secreted ligand is encoded by this gene. This class of ligands binds different *TGF-β* receptors, causing the recruitment and activation of transcription factors from the SMAD family that control gene expression. The encoded preproprotein is either found in a latent form made up of a mature peptide homodimer, a LAP homodimer, and a latent *TGF-β* binding protein, or it is found

in an active form made up primarily of the mature peptide homodimer. The mature peptide can combine with other *TGF-β* family members to create heterodimers. The production and activation of other growth factors, including interferon-gamma and tumor necrosis factor, can be modulated by this encoded protein, which also controls cell proliferation, differentiation, and growth [76]. The C allele of *TGF-β1* gene in codon 25: + 915*G/C was linked to greater risk of T2DM polymorphism, while the G allele appears to offer protection against the disease. However, Hussein found the risk of T2DM was increased in GG and CC genotypes; this risk was not observed in the GC genotype [77]. The study by Nuhiar suggests TGFβ1 gene polymorphisms to be implicated in the incidence of T2DM in the population of Thi-Qar [79].

TCF7L2: encodes a transcription factor with a high mobility group (HMG) box that is essential for the Wnt signaling pathway. The protein has been linked to the regulation of blood sugar levels. An increased risk of T2D is linked to genetic variations of this gene. For this gene, many transcript variants have been discovered that encode various isoforms [79]. Genotyping of 212 participants was conducted using a cost- and time-effective, high-throughput tetra-primer amplification refractory mutation system-polymerase chain reaction (Tetra ARMS-PCR) assay. The results indicate an association between *TCF7L2* rs7903146 polymorphisms and the risk of T2DM. Among Kurdish Iraqi people, the T allele appears to promote the individual's susceptibility of developing T2DM [80]. None of the controls in Omran study expressed the TT genotype of rs12255372(G/T), which was determined to be an important risk factor for developing T2DM [81]. According to Hassan (2018), the rs12255372 (G/T) polymorphism makes the Al Najaf population vulnerable to T2DM [82]. Data from Mohammed (2021), point to a robust relationship between rs7908486 and obesity; this gene could be used as an effective early detection biomarker of obesity [83]. Ahmed (2019), claim that *TCF7L2* gene genetic polymorphisms were influential in females in Iraq developing T2DM. In contrast, data obtained by Abdullah, failed to find a role for *TCF7L2* gene polymorphism rs4506565 T/A, with no significant differences being detected in any of the codominant, dominant, over dominant, recessive, and additive models. Of the parameters considered by the dominant model, only age shows a significant difference [84, 85].

VCAM-1: It is a member of the Ig superfamily that produces a cell surface sialoglycoprotein when the endothelium is stimulated by cytokines. This type I membrane protein may contribute to the development of rheumatoid arthritis and atherosclerosis by mediating leukocyte-endothelial cell adhesion and signal transmission [86]. The findings of Salman (2017), Study indicate that A/G genotype was more prevalent in the control group than the patient group. Furthermore, he found that compared to the A allele, the G allele of the *VCAM-1* (rs3783605 A: G) SNP made a greater contribution to causing T2DM [88]; thus, among the population of Iraq, it could be as a potent risk factor for T2DM.

PON1: Discovered for its detoxifying potential, serum paraoxonase (*PON1*) is presumed to counteract organophosphorus compound toxicity. The lower activity of *PON1* is thought to increase susceptibility to poisoning. Rabbit *PON1* injections in rodents demonstrated protection against paraoxon and chlorpyrifos oxon toxicity, supported by recent *PON1* knockout mouse studies. Knockout mice showed heightened sensitivity to these toxins due to the loss of liver *PON1* activity [88]. Moreover, *PON1*, an antioxidant enzyme in human serum, safeguards low-density lipoproteins from oxidative stress. Investigating *PON1* 55 methionine (M)/leucine (L) polymorphisms in T2DM revealed an association between the *PON1* L55M polymorphism and smoking status in T2DM patients and healthy individuals, implying its role in oxidative stress modulation [89].

Vitamin D receptor (*VDR*) gene: The calcitriol (1,25(OH)2D3) and its analogs have a variety of 36 biological effects, and the vitamin D receptor (*VDR*), a member of the nuclear receptor 35 superfamily of transcriptional regulators, mediates these actions. Pregnane X receptor (PXR; both are members of the NR1I subfamily 39) and *VDR* 37 have been hypothesized to result from duplication of an ancestral 38 genes. The many functions of vitamin D in cell growth and differentiation, immunology [90]. While Al-Kashwan (2019), did not find any association between *VDR* TaqI polymorphism and T2DM in the Iraqi population [91]. The results of the current study indicate a correlation between the incidence of T2DM and the BsmI rs1544410 SNP. We also noted that the risk of T2DM increased in the presence of the FokI rs2228570 SNP; this polymorphism is implicated in low serum levels of vitamin D [92]. The effect of polymorphic *VDR* has also been identified by Najjar (2020), who suggest that the risk of T2DM and associated neuropathies are elevated by the T allele of TaqI and F allele of FokI polymorphisms in the *VDR* gene. Both TaqI and FokI could be exploited as predictive markers for neuropathy and other complications of T2DM [93].

WFS1: This gene encodes a transmembrane protein primarily located in the endoplasmic reticulum and expressed widely, with significant levels in the brain, pancreas, heart, and insulinoma beta-cell lines. Genetic mutations in this gene are linked to Wolfram syndrome, or DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness), an autosomal recessive

disorder affecting the central nervous system. Autosomal dominant deafness 6 (DFNA6), also known as DFNA14 or DFNA38, can also arise due to mutations in this gene. Various transcript variants resulting from alternative splicing have been identified [94]. While WFS1's influence on the development of T2DM is notable, particularly in relation to the GA vs GG alleles, its impact has not been uniformly demonstrated in all instances [95].

Demographic genotype analysis

In this study, a comprehensive genetic analysis was undertaken to unravel the intricate landscape of genetic factors associated with T2DM within the Iraqi population. Notably, our approach encompassed the implementation of a diverse array of polymerase chain reaction (PCR)-based genotyping methods, reflecting our commitment to methodological rigor and comprehensive investigation. Figure 3 illustrates the distribution of the genotype across all the selected studies. The judicious utilization of multiple PCR-based genotyping methods brings forth several scientific implications, bolstering the robustness and reliability of our genetic analysis.

The salient implications of this approach are elucidated below, highlighting their significance within the context of our study:

- Methodological Diversity and Robustness: The adoption of various PCR-based techniques, including PCR–RFLP, PCR-ARMS, RT-PCR, PCR-Taqman, Conventional-PCR, PCR-HRM, PCR-SSCP, PCR-SSP, and Sanger-PCR, underscores our meticulous pursuit of methodological diversity. By employing multiple techniques, each with distinct attributes and sensitivities, we ensured a well-rounded and thorough exploration of genetic variations. This methodological pluralism mitigates the potential biases intrinsic to any single approach and safeguards against spurious associations or erroneous conclusions.
- Validation of Genetic Associations:The recurrent application of established techniques such as PCR–RFLP and PCR-ARMS fortifies the validity of the genetic associations identified in our study. The consistent reaffirmation of these associations across diverse genotyping methods attenuates the likelihood of coincidental findings or method-specific artifacts. This harmonious convergence across techniques accentuates the credibility of the genetic associations elucidated within our study population.
- Encompassing Genetic Heterogeneity: Each PCR-based method has a predilection for detecting specific types of genetic variations, be it single nucleotide polymorphisms (SNPs), insertions, deletions, or copy number variations. Our strategic use of a plethora of techniques broadened our coverage of genetic diversity, thereby enabling a more comprehensive depiction of the genetic landscape underpinning T2DM within our cohort.
- Cross-Validation of Findings: The congruence of outcomes across disparate genotyping methods affords a higher degree of confidence in the genetic associa-

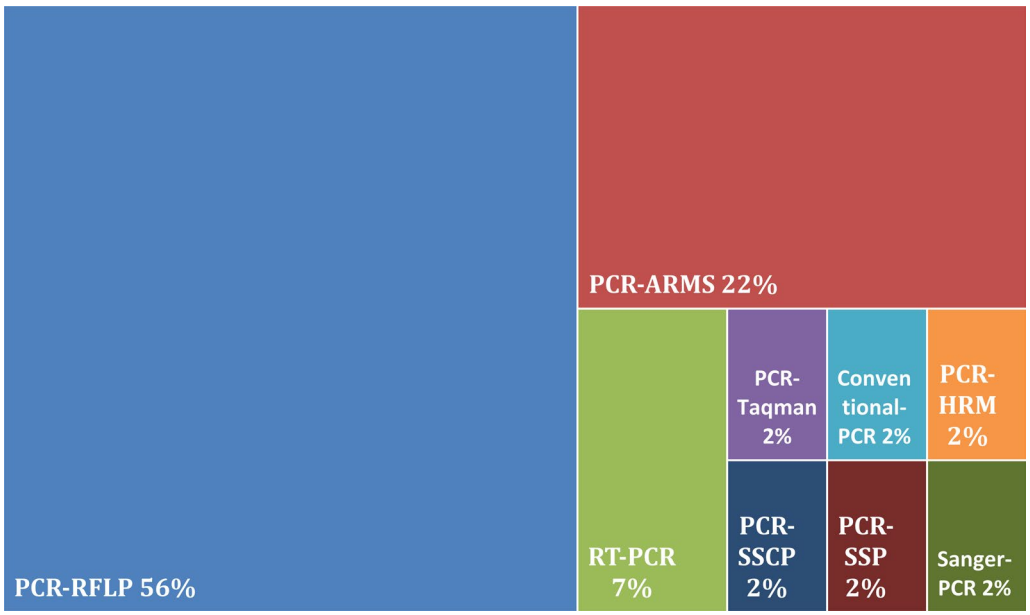

Fig. 3 Treemap of the Genotype methods observed in the selected studies

tions discerned. The convergence of results observed through varied techniques minimizes the potential for spurious or idiosyncratic findings, thereby reinforcing the authenticity of our genetic inferences.

- Augmentation of Replicability and Generalizability: By harmonizing multiple PCR-based methods, our study is primed for facile replication and comparability with analogous investigations. The consistency of our findings across multiple genotyping techniques fosters a more unified platform for gauging the consistency of our results across diverse populations, advancing the generalizability of our genetic insights.
- Elevated Conclusiveness and Transparency: Our judicious utilization of diverse genotyping methods augments the definitiveness of our study's conclusions. These conclusions are bestowed with a heightened robustness that transcends the limitations inherent to individual techniques. Furthermore, this methodological transparency underpins our commitment to rigorous scientific practice and enhances the comprehensibility of our methodologies for peers and researchers.

The integrative application of a spectrum of PCR-based genotyping methods serves as a cornerstone of our genetic analysis framework. This approach enriches the credibility, comprehensiveness, and reliability of our genetic inferences, positioning our study as a pivotal contribution to the intricate domain of genetic research surrounding T2DM within the Iraqi populace.

The investigation into genetic determinants of T2DMin the Iraqi population involved a comprehensive examination of genetic variations across multiple cities. Employing diverse PCR-based genotyping methods, we aimed to elucidate the interplay between genetics and regional demographics within specific Iraqi urban centers. Genotyping efforts were concentrated in various Iraqi cities, each contributing to the overall genetic portrait. The following cities were investigated:

- Babylon: Genetic profiling in Babylon involved the application of PCR-ARMS and PCR–RFLP techniques, leveraging their capabilities for targeted variation detection.
- Baghdad: The capital city, Baghdad, underwent extensive genetic analysis utilizing a range of PCR-based techniques, including Conventional-PCR, PCR-ARMS, PCR-HRM, PCR–RFLP, PCR-SSP, and PCR-Taqman, facilitating a comprehensive genetic assessment.
- Basra: Genetic attributes within Basra were probed using the PCR–RFLP method, known for its applicability in allelic discrimination.
- Diwaniyah and Diyala: The genetic landscapes of Diwaniyah and Diyala were explored through PCR–RFLP and RT-PCR methods, both suited for robust allele identification.
- Erbil: Genetic exploration in Erbil encompassed PCR-ARMS, PCR–RFLP, and Sanger-PCR techniques, allowing for meticulous genetic characterization.
- Kerbala (Karbala): Kerbala's genetic makeup was deciphered employing PCR-ARMS, PCR–RFLP, PCR-SSCP, and RT-PCR methods, offering a comprehensive genetic insight.
- Kut, Najaf, and Thi-Qar: Kut, Najaf, and Thi-Qar were investigated utilizing PCR-ARMS and PCR–RFLP methodologies, suited for targeted allelic analysis.

The genetic data acquired from each city were integrated and evaluated, enabling the identification of allelic variations associated with T2DM within distinct urban contexts. This integrative approach facilitated the correlation of genetic findings with regional demographics, contributing to a nuanced understanding of the genetic underpinnings of T2DM across Iraqi cities. By employing a spectrum of genotyping techniques and encompassing diverse urban locales, our methodology enhances the reliability and generalizability of our genetic findings. The comprehensive approach mitigates potential biases associated with single-method investigations, bolstering the authenticity of our genetic inferences.

The distribution of patient and control populations varies considerably across Iraqi cities, reflecting the diverse demographic attributes inherent to each urban locale. The following observations arise from the data illustrated in Fig. 4.

Baghdad and Najaf emerge as key focal points, exhibiting substantial patient populations of 1490 and 6443, respectively. These cities hold prominence not only due to their large patient cohorts but also due to their considerably larger control populations of 684 and 3165, respectively. The magnitude of these populations underscores their significance in understanding T2DM prevalence and its demographic nuances. Erbil and Kerbala also exhibit notable patient populations, numbering 524 and 908, respectively. These cities, along with their respective control groups of 256 and 432, contribute substantially to the overall study demography. Their significant representation lends depth to our understanding of T2DM within these regions. Diwaniyah and Kut showcase patient populations of 500 and 150, respectively, with corresponding control groups of 250 and 75. These cities provide insights into T2DM prevalence in more moderate sample sizes, offering a nuanced perspective on

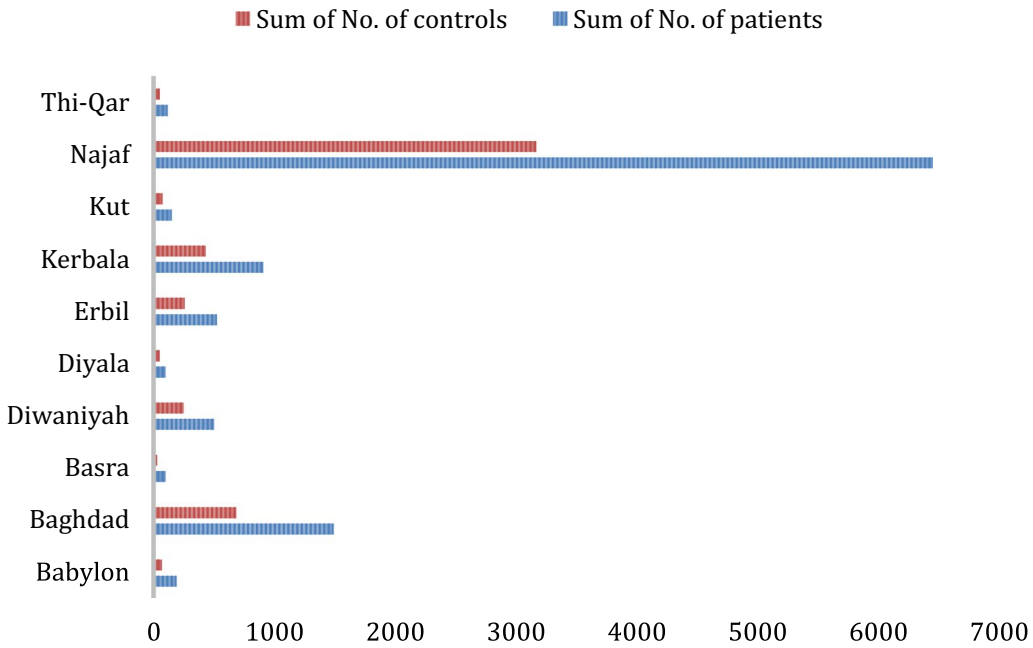

Fig. 4 Total number of population of the studies versus the associated city

the disease's local impact. Cities such as Babylon, Basra, Diyala, and Thi-Qar exhibit more modest patient and control populations. While the patient populations in these locales range from 100 to 190, the control groups range from 30 to 52. These cities, while smaller in scale, contribute to the overall mosaic of T2DM demographics within the study.

The demographic distribution of patient and control populations across these Iraqi cities holds significance for both this study and future research endeavors. The variations in population sizes underscore the inherent demographic diversity across the nation, emphasizing the need for localized research and intervention strategies. The larger patient populations in cities like Baghdad, Najaf, Erbil, and Kerbala call for heightened scrutiny, potentially revealing insights into regional risk factors, genetic predispositions, and healthcare disparities.

Sensitivity analysis

The forest plot, serving as a visual representation of the odds ratios and their associated confidence intervals, presents an intricate picture of the relationship between identified genes and T2DM within the Iraqi population. In this analysis, we delve into the nuances of the forest plot to discern patterns, disparities, and the overall impact of these genetic associations on T2DM. The forest plot is illustrated in Fig. 5. Observing the arrangement of studies on the forest plot, a prevailing trend emerges as a considerable number of studies appear to skew over the null effect line (odds ratio of 1). This clustering of studies around the null effect line suggests that the majority of the identified genes might not exhibit a statistically significant association with the development of T2DM within the Iraqi population. This observation underscores the importance of scrutinizing individual studies and their collective implications.

Despite this trend, the calculated overall odds ratio of 2.34 provides insight into the potential association between the identified genes and T2DM. This value suggests a tendency towards a higher odds of T2DM among the studied population in relation to the identified genes. However, the presence of studies skewing around the null effect line necessitates cautious interpretation of this overall estimate, urging us to investigate further to elucidate the underlying dynamics. Crucially, within the ensemble of studies, a subset of 6 studies holds a notable weight of approximately 7.6, potentially exerting a substantial influence on the overall effect estimate. While these high-weight studies contribute to the broader understanding of the genetic associations, it is imperative to recognize that their impact must be weighed in conjunction with the broader spectrum of studies, many of which do not align with a clear trend towards statistical significance. Moreover, the adoption of a logarithmic scale of 10 in the forest plot introduces a layer of complexity to the visualization. This logarithmic transformation compresses the effect sizes, leading to an altered perception of differences between studies. It underscores the necessity of meticulous interpretation to grasp the

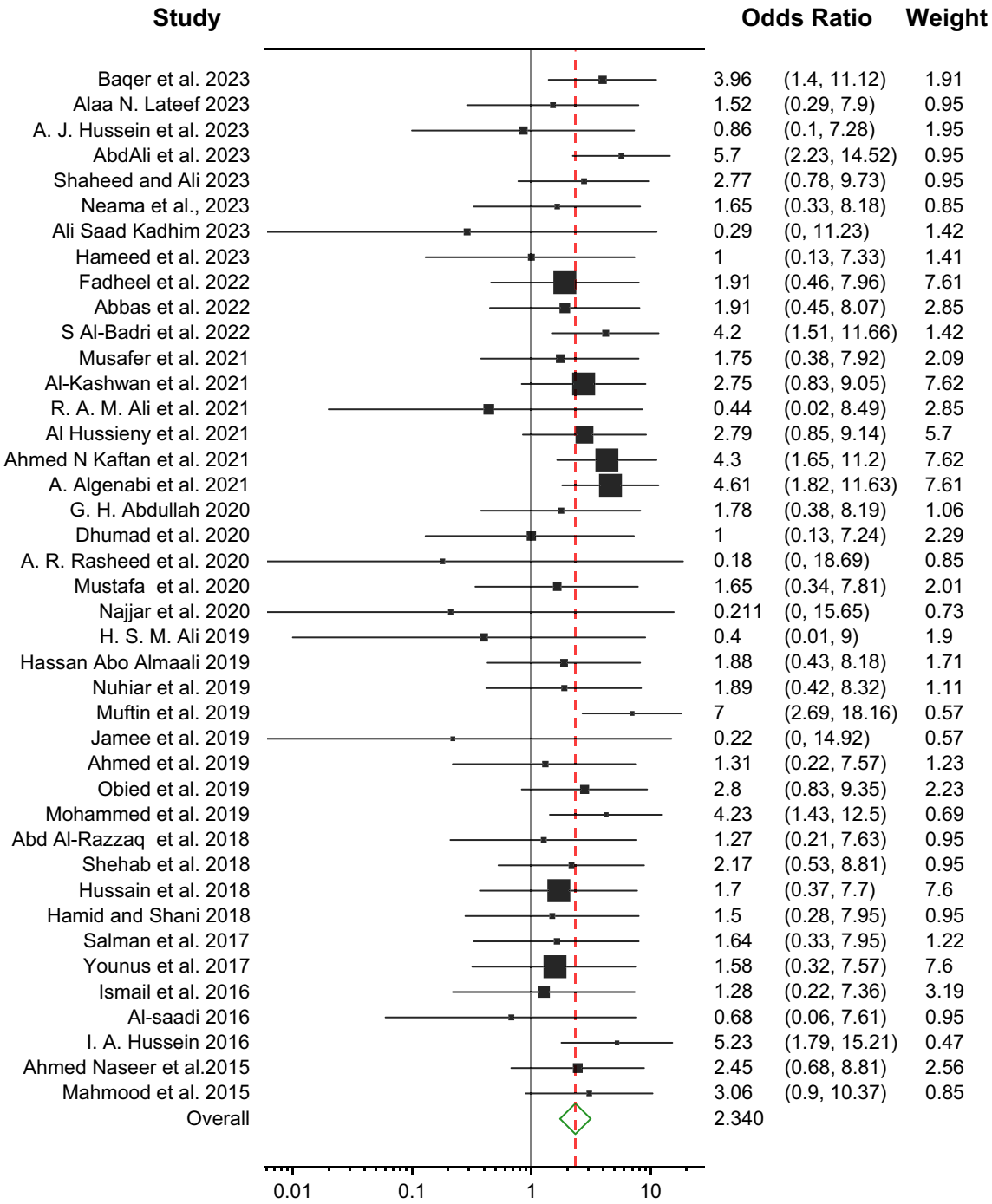

Fig. 5 Forest plot depicting the studies presenting the genetic associations with T2DM

true implications of genetic associations on T2DM within the Iraqi population.

Notably, the forest plot also highlights three studies with odds ratios lower than 1 (0.22, 0.18, 0.21). However, the presence of wide confidence intervals (+14.92, +18, +15.65) accompanying these odds ratios underlines the substantial uncertainty in their effect estimates. The considerable range of these confidence intervals accentuates the need for cautious interpretation, suggesting that these genes might lack precision in their association with T2DM. In conclusion, the forest plot paints a multifaceted portrait of the genetic associations

with T2DM within the Iraqi population. While the majority of studies do not appear to exhibit a statistically significant link, the overall odds ratio of 2.34 hints at a potential association. The presence of high-weight studies, wide confidence intervals, and the logarithmic scale all contribute to the intricate nature of the analysis. As we navigate these complexities, we acknowledge the significance of a meticulous and holistic understanding of genetic associations with T2DM, striving for a comprehensive grasp of their implications for clinical practice and future research endeavors.

Conclusion

In conclusion, this meta-analysis provides a comprehensive review of the genetic variants associated with T2DM in the Iraqi population. Through the analysis of data obtained from over 7893 patients and 5064 control participants, we have identified 31 genes that have a robust association with the disease. Our findings are consistent with earlier systematic reviews that have noted the significant effects of particular genotypes on T2DM. Our study has answered the research questions we posed, which were: (1) What are the genetic variants associated with T2DM in the Iraqi population? (2) Which of the identified genetic variants exacerbate the effects of T2DM? (3) Which of the identified genetic variants exert a significant protection against T2DM? We have identified several genetic SNPs, which is determined to be a risk factor for different complications in patients with T2DM.

These findings have significant implications for future research, as they may be useful in identifying potential means of predicting or identifying T2DM through simple, non-invasive tests. Moreover, since there is presently limited knowledge about managing T2DM or support for patients, the data provided here may assist the government in making superior healthcare policies that benefit the people of Iraq. It is worth noting that this study has some limitations. Firstly, there was a lack of uniformity in the methods used to collect the genetic data, which may have affected the consistency and accuracy of the results. Additionally, the sample size of control participants was relatively small compared to that of the patient group, which may have influenced the statistical power of the analysis. Finally, our study was limited to genetic factors and did not explore environmental or lifestyle factors that may also contribute to T2DM.

This meta-analysis provides valuable insights into the genetic SNPs associated with T2DM in the Iraqi population. The results of this study may aid in the development of strategies for preventing, identifying, and managing T2DM in the future. Further research in this area, with larger sample sizes and a more comprehensive approach, may provide a more nuanced understanding of the genetic and environmental factors that contribute to T2DM in the Iraqi population.

Abbreviations

T2DM	Type 2 diabetes mellitus
CHD	Coronary heart disease
CVDs	Cardiovascular diseases
DN	Diabetic nephropathy
CAD	Coronary artery disease
DFU	Diabetic foot ulcer

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Author contributions

KNJM: Conceived and designed the study, analyzed and interpreted the data. MR: Conducted the literature search, screened and selected the studies, and contributed to the data analysis and interpretation. This author also drafted the manuscript. ASC: Helped in reviewing the manuscript. SS: Helped in reviewing the manuscript. MRRA: Helped in reviewing the manuscript. FH: Contributed to the data interpretation and critically revised the manuscript.

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Availability of data and materials

All data and material used in this study are cited and referenced accordingly in the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable as this study is a meta-analysis and review of published literature.

Consent for publication

Not applicable as this study is a meta-analysis and review of published literature.

Competing interests

The authors declare that they have no competing interests.

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