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REVIEW ARTICLE

Established type 2 diabetes-susceptibility genetic variants in Saudi ethnicity: a mini-systematic review

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ABSTRACT

Background: Type 2 diabetes (T2D) is a polygenic and multi-factorial complex disease. The significant challenge of finding genetic markers that could be used to predict T2D risk remains unresolved. Saudi Arabia is one of several ethnicities with a high prevalence rate of T2D. A large number of studies have been performed that explored genetic factors associated with T2D risk. In this work, we conducted a systematic review of published studies on T2D genetic markers in the Saudi population.

Methodology: Multiple databases were employed in the literature review, which focused on studies that either reported the association or non-association of a genetic marker with T2D risk. Using appropriate search terms, we collected, analyzed, and selected 428 articles published between the years of 2000 and 2018; of these, 18 articles reported a total of 67 polymorphisms in 46 genes that are strongly linked to T2D in the Saudi population.

Results: Most of the relevant studies used genotyping as the primary methodology to identify genetic markers of T2D. Most of these studies were published between the years 2012 and 2017. A total of 23 polymorphisms in 17 genes were found to be associated with T2D risk in the Saudi population: *KCNJ11*, *PPARG2*, *IRS1*, *VDE*, *WFS1*, *JAZF1*, *CDKN2A/B*, *TCF7L2*, *KCNQ1*, *HNF4A*, *DUSP9*, *APOE*, *HNF1A*, *SLC30A8*, *APOC3*, *SNAP25*, and *ACE*.

Keywords: Type 2 diabetes, genetics, Saudi Arabia.

Introduction

Type 2 diabetes mellitus (T2D) is one of the leading causes of death worldwide and Saudi Arabia has a high prevalence of this disease. Although previous studies strongly support that lifestyle and environmental factors play a crucial role in T2D development, it is assumed that genetic factors also have a serious impact on disease development. According to the International Diabetes Federation, there are 425 million people worldwide affected by diabetes in 2017 and one in two adults are undiagnosed (212 million) and are, therefore, at higher risk of developing diabetic complications (1). Also, one in six births is reported to be affected by hyperglycemia during pregnancy, which is associated with an increased risk of the infants developing T2D in the future (1). In 2017, Saudi Arabia was ranked eighth among countries known to have high prevalence rates of diabetes, with 3,487,288 reported cases of diabetes (1,2). One-quarter (25.4%) of the Saudi population has abnormal glucose levels and almost half (40.3%) of Saudi diabetic patients remain unaware of their disease (3). The high prevalence of diabetes in the Saudi ethnic group could be due to lifestyle changes and genetic factors along with the high consanguinity rate (56%) seen in this community (4). Throughout the world, the highest prevalence of diabetes is anticipated to occur in the Middle East and North Africa due to rapid economic development, urbanization, and changes in lifestyle (5). There has been a wide range of difference observed in Saudi ethnicity when we look into the prevalence trend. Approximately 0.9 million people were diagnosed with diabetes in 1992, which reached over 2.5 million people in 2010, which is a 2.7-fold increase within two decades. Studies from 2015 reported an approximately 10-fold increase in the number of diabetic patients who visited family and medical clinics across Saudi Arabia (5). This increased

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rate of diabetes could be linked to increases in obesity and an aging population. Several studies revealed that the prevalence of diabetes was increasing as a function of age in the Saudi community, with higher prevalence in males as compared to females (6,7). Genome-wide association studies (GWAS) in the Western world have reported more than 150 loci associated with T2D risk. However, there is very limited information regarding the role of these loci in the Saudi Arabian population. Extensive efforts have been made to study genetic variants of complex diseases using single nucleotide polymorphisms (SNPs). The International HapMap Project, carried out as a part of the Human Genome Project, provides information concerning more than 1 million SNPs in the human genome, which has contributed tremendously to advancements in genetic screening technology (8). Advancements in genotyping technologies have generated more information regarding SNPs and their association with a particular type of disease. The last decade has witnessed an exponential growth in the number of genetic studies that addressed T2D risk, including GWAS, genotyping arrays, and next-generation sequencing studies (9). Since the first GWAS study of T2D risk in 2007, this type of study has been able to report an increasing number of genetic factors associated with T2D risk. In 2016, there were 75 independent genetic loci reported to be associated with T2D risk and the current number of genetic loci associated with T2D risk has exceeded 80 (9). However, much remains to be explored, especially the mechanisms used by these variants to exert their effects on the pathogenesis of T2D. This systematic review evaluated studies that demonstrated an association between genetic factors and T2D risk among the Saudi population and lists the relevant genes and polymorphisms.

Materials and Methods

Study design

This study included genetic association studies conducted on Saudi populations residing in Saudi Arabia, which used diagnosed diabetes and/or markers of glucose homeostasis as outcomes. Studies had to meet the following criteria to be included: (i) original papers containing independent data, (ii) case-control or cohort studies, and (iii) sufficient data to provide statistical significance for polymorphisms tested [using parameters such as odds ratio (OR) with a confidence interval (CI)]. A filtration procedure was used to remove duplicates, irrelevant publications, and studies conducted in Arab research institutions that used non-Saudi subjects (Figure 1). The online databases PubMed and Web of Science were used to perform a literature search for publications published between January 2000 and August 2018, without any date or language restrictions. We used a combination of relevant search terms such as "diabetes mellitus" OR "type 2 diabetes" AND "genetics" OR "genetic marker" OR "genetic polymorphism" OR "single nucleotide polymorphism" OR "polymorphism" OR "gene" OR "allele" AND "Saudi Arabia" OR Saudi Arab. We independently identified publications and systematically screened titles, abstracts, and full texts of the collected publications (Figure 1). The reference list of the collected publications was also cross-checked and validated using Web of Science.

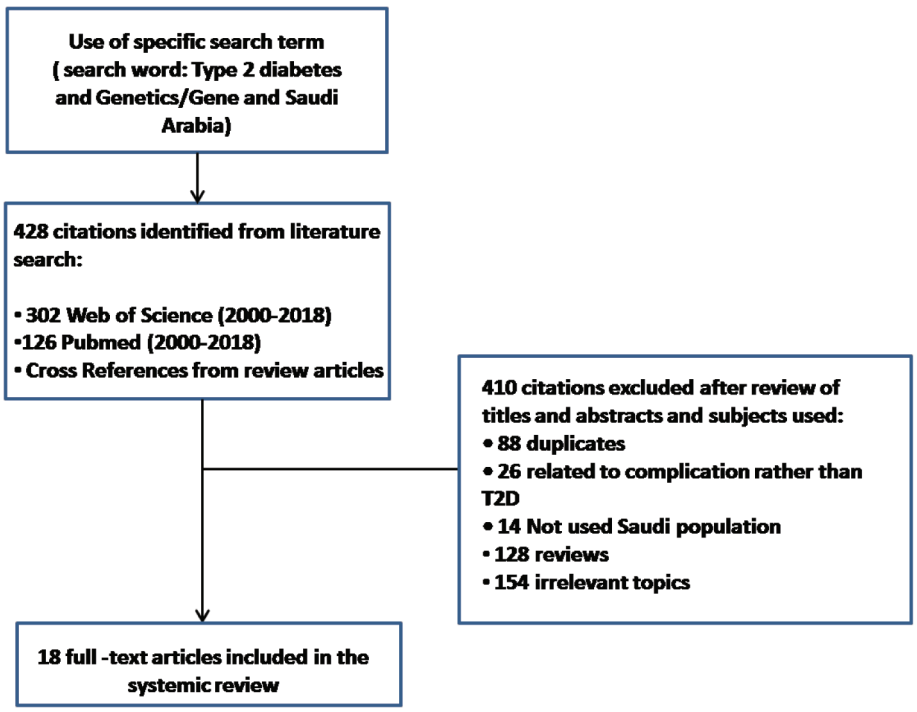

Figure 1. *Selection process of studies used in the systematic review.*

Data collection

A systematic literature search was conducted to identify publications reporting genetic factors or polymorphisms associated with T2D risk in Saudi Arabia. The majority of studies were published between 2012 and 2017. Selected publications focused specifically on the association between genetic polymorphisms and development of T2D or the non-association of genetic polymorphisms with the development of T2D. The initial literature search was based on title, abstract, and study subjects resulting in a total of 428 publications, which then underwent full-text screening. Also, the collected publications underwent one more round of screening in which duplicates, publications related to diabetic complications other than T2D, publications that did not use Saudi subjects, and irrelevant studies were excluded. The filtration process removed 410 publications, resulting in 18 publications that were used for the systematic review.

Results

The majority of studies (10–27) were published between the years 2012 and 2017 (15–18,22,24). The number of participants per study ranged from 90 (21) to 2,419 (19) and the age of participants ranged from 20 to 80 years. The TaqMan genotyping assay was the most common methodology used for genetic screening in the publications analyzed (18,19,21,22,25,27). Five studies used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) (13,14,16,20,24) and two studies used molecular beacon-based real-time PCR (11,12). Other technologies included pyro-sequencing (10), real-time PCR (15), amplification-refractory mutation system-polymerase chain reaction (ARMS-PCR) (23), Kompetitive allele-specific polymerase chain reaction (KASPar method) (17), and PCR using an insertion specific primer (26). A total of 67 polymorphisms in 46 genes were investigated in the studies (Table 1). Studies that reported the association of genetic markers with T2D are shown in Table 1. One SNP per gene was observed to be significantly associated with T2D risk in the following genes: *KCNJ11, VDR, WFS1, CDKN2A/2B,* and *HHNF4*. Two SNPs in the genes *IRS1, JAZF1, KCNQ1, APOE* and three SNPs in *TCF7L2* were observed to be significantly associated with T2D risk. Forty-four SNPs in 37 genes were not associated with T2D or measurements of glycemia (Table 1). All studies used statistical tools to validate their results. The 23 polymorphisms observed to be strongly associated with T2D risk in the Saudi population were mapped to a total of 13 chromosomes (Figure 2).

Table 1. *Genetic variants linked with a higher risk of T2Din the Saudi population.(Continued)*

Tested gene	Type of study	Chromosome location	Gene function	Risk allele	Association with T2D	Year and Reference
KCNJ11	Original research (Genotyping)	11	The protein encoded by this gene is an integral membrane protein and inward-rectifier type potassium channel.	rs5219 rs5215	Associated Non-associated	2008 [11] 2014 [17]
PPAR-GAMMA2	Original research (PCR-RFLP)	3	Regulation of transcription; regulation of adipocyte differentiation	rs1801282	Associated	2006 [12]
IRS1	Original research (PCR-RFLP)	2	Phosphorylation of insulin receptor tyrosine kinase and control of various cellular processes by insulin	rs1801278 rs243641 Gly972Arg polymorphism	Associated Non-associated	2014 [13] 2015 [14]
VDR	Original research (genotyping)	12	Encodes nuclear hormone receptor for vitamin D3 and involved in mineral metabolism though the receptor regulates a variety of other metabolic pathway.	rs10735810 rs10735810 rs1544410	Associated Non-associated Non-associated	2014 [15]
WFS1	Original research (genotyping	4	Participates in the regulation of cellular Ca(2+) homeostasis.	rs1801214	Associated	2014 [17]
JAZF1	Original research (genotyping Original research (PCR-RFLP)	7	Plays a role in glucose homeostasis by improving glucose metabolism and insulin sensitivity.	rs849134 rs864745	Associated Associated	2014 [17] 2015 [24]

(Continued)

Tested gene	Type of study	Chromosome location	Gene function	Risk allele	Association with T2D	Year and Reference
CDKN2A/B	Original research (genotyping	9	Plays a crucial role in cycle regulation process.	rs10965250	Associated	2014 [17]
TCF7L2	Original research (genotyping)	10	Important for blood glucose homeostasis and regulation of proglucagon via the Wnt signaling pathway.	rs7903146	Associated	2014 [17]
				rs12255372	Associated	2015 [23]
				rs4506565	Associated	2015 [23]
	Meta analysis			rs12255372	Non-associated	2008 [10]
	Original research (genotyping)			rs7903146	Non-associated	2015 [23]
KCNQ1	Original research (genotyping)	11	Regulates voltage-gated potassium channel required for depolarization phase of the cardiac action potential.	rs231362	Associated	2014 [17]
				rs163184	Associated	2014 [17]
				rs151290	Non-associated	2018 [27]
				rs2237895	Non-associated	2018 [27]
HNF4A	Original research (genotyping)	20	Involved in development of the liver, kidney, and intestine.	rs4812829	Associated	2014 [17]
DUSP9	Original research (genotyping)	Chromosome X	Involved in cellular proliferation and differentiation.	rs5945326	Associated	2014 [17]
APOE	Original research (genotyping)	19	Mediates the binding, internalization, and catabolism of lipoprotein particles	rs429358	Associated	2014 [18]
				rs7412	Associated	2014 [18]
HNF1A	Original research (sequencing)	12	It is a transcriptional activator that regulates the tissue specific expression of multiple genes, especially in pancreatic islet cells and in liver.	rs2259820	Associated	2014 [19]
	Original research (genotyping)			rs7957197	Not associated	2014 [17]
SLC30A8	Original research (genotyping)	8	Facilitates the accumulation of zinc from the cytoplasm into intracellular vesicles, being a zinc-efflux transporter.	rs13266634	Associated	2014 [21]
				rs3802177	Not associated	2014 [17]
APOC3	Original research (genotyping)	11	This protein has been shown to promote the secretion of VLDL1, inhibit lipoprotein lipase enzyme activity, and delay catabolism of TRL remnants.	*AP*3238C>G	Associated	2015 [22]
				-482C>T	Not associated	2015 [22]
SNAP25	Original research (genotyping)	20	Involved in the molecular regulation of neurotransmitter release. May play an important role in the synaptic function of specific neuronal systems.	rs363050	Associated	2016 [25]
				rs363039	Not associated	2016 [25]
ACE	Original research (genotyping)	17	It cleaves a C-terminal dipeptide from angiotensin I to create the vasoconstrictor peptide, angiotensin II.	ACE insertion deletion (I/D) polymorphism rs1799752	Associated	2017 [26]
ABCA1	Original research (PCR-RFLP)	9	Transport various molecules across extra- and intracellular membranes.	rs1800977	Not associated protective in nature	2013 [16]
NOTCH2	Original research (genotyping)	1	Notch family members play a role in a variety of developmental processes by controlling cell fate decisions.	rs10923931	Not associated	2014 [17]
THADA	Original research (genotyping)	2	The encoded protein is likely involved in the death receptor pathway and apoptosis.	rs11899863	Not associated	2014 [17]

(Continued)

Tested gene	Type of study	Chromosome location	Gene function	Risk allele	Association with T2D	Year and Reference
BCL11A	Original research (genotyping)	2	May play important roles in leukemogenesis and hematopoiesis. Essential factor in lymphopoiesis required for B-cell formation in fetal liver. May function as a modulator of the transcriptional repression activity of ARP1.	rs243021	Not associated	2014 [17]
GRB14	Original research (genotyping)	2	Involved in signaling pathways that regulate growth and metabolism	rs3923113	Not associated	2014 [17]
PPARG	Original research (genotyping)	3	Key regulator of adipocyte differentiation and glucose homeostasis.	rs13081389	Not associated	2014 [17]
ADAMTS9	Original research (genotyping)	3	Involved in cleavage of proteoglycans, the control of organ shape during development, and the inhibition of angiogenesis.	rs6795735	Not associated	2014 [17]
ST6GAL1	Original research (genotyping)	3	Involved in the generation of the cell-surface carbohydrate determinants and differentiation antigens HB-6, CD75, and CD76.	rs16861329	Not associated	2014 [17]
ZBED3	Original research (genotyping)	5	Acts as a positive regulator in the activation of the canonical Wnt/beta-catenin signaling pathway by stabilizing cytoplasmic beta-catenin. Involved in transcription activation of Wnt target gene expression.	rs4457053	Not associated	2014 [17]
CDKAL1	Original research (genotyping)	6	The protein encoded by this gene is a member of the methylthiotransferase family. The function of this gene is not known. Genome-wide association studies have linked single nucleotide polymorphisms in an intron of this gene with susceptibilty to type 2 diabetes.	rs10440833	Not associated	2014 [17]
KLF14	Original research (genotyping)	7	This gene exhibits imprinted expression from the maternal allele in embryonic and extra-embryonic tissues.	rs972283	Not associated	2014 [17]
TP53INP1	Original research (genotyping)	8	Ant proliferative and proapoptotic protein involved in cell stress response which acts as a dual regulator of transcription and autophagy.	rs896854	Not associated	2014 [17]
ADAMTS9	Original research (genotyping)	3	Involved in cleavage of proteoglycans, the control of organ shape during development, and the inhibition of angiogenesis.	rs6795735	Not associated	2014 [17]
ST6GAL1	Original research (genotyping)	3	Involved in the generation of the cell-surface carbohydrate determinants and differentiation antigens HB-6, CD75, and CD76.	rs16861329	Not associated	2014 [17]
ZBED3	Original research (genotyping)	5	Acts as a positive regulator in the activation of the canonical Wnt/beta-catenin signaling pathway by stabilizing cytoplasmic beta-catenin. Involved in transcription activation of Wnt target gene expression.	rs4457053	Not associated	2014 [17]
CDKAL1	Original research (genotyping)	6	The protein encoded by this gene is a member of the methylthiotransferase family. The function of this gene is not known. Genome-wide association studies have linked single nucleotide polymorphisms in an intron of this gene with susceptibility to type 2 diabetes.	rs10440833	Not associated	2014 [17]

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Tested gene	Type of study	Chromosome location	Gene function	Risk allele	Association with T2D	Year and Reference
KLF14	Original research (genotyping)	7	This gene exhibits imprinted expression from the maternal allele in embryonic and extra-embryonic tissues.	rs972283	Not associated	2014 [17]
TP53INP1	Original research (genotyping)	8	Ant proliferative and proapoptotic protein involved in cell stress response which acts as a dual regulator of transcription and autophagy.	rs896854	Not associated	2014 [17]
CHCHD9	Original research (genotyping)	9	CHCHD2P9 (Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 2 Pseudogene 9) is a Pseudogene.	rs13292136	Not associated	2014 [17]
CDC123	Original research (genotyping)	10	Required for S phase entry of the cell cycle.	rs12779790	Not associated	2014 [17]
VPS26A	Original research (genotyping)	10	Involved in retrograde transport of proteins from endosomes to the trans-Golgi network.	rs1802295	Not associated	2014 [17]
HHEX	Original research (genotyping)	10	Its expression in specific hematopoietic lineages suggests that this protein may play a role in hematopoietic differentiation	rs5015480	Not Associated	2014 [17]
CENTD2/ ARAP1	Original research (genotyping)	11	It is thought to regulate the cell-specific trafficking of a receptor protein involved in apoptosis.	rs1552224	Not associated	2014 [17]
MTNR1B	Original research (genotyping)	11	It is thought to participate in light-dependent functions in the retina and may be involved in the neurobiological effects of melatonin	rs1387153	Not associated	2014 [17]
HMGA2	Original research (genotyping)	12	Functions as a transcriptional regulator. Functions in cell cycle regulation through CCNA2. Plays an important role in chromosome condensation during the meiotic G2/M transition of spermatocytes	rs1531343	Not associated	2014 [17]
TSPAN8	Original research (genotyping) Original research (PCR-RFLP)	12	The proteins mediate signal transduction events that play a role in the regulation of cell development, activation, growth and motility.	rs4760790 rs1552224	Not associated Not associated	2014 [17] 2014 [17]
HMG20A	Original research (genotyping)	15	Plays a role in neuronal differentiation as chromatin-associated protein.	rs7178572	Not associated	2014 [17]
ZFAND6	Original research (genotyping)	15	Involved in regulation of TNF-alpha induced NF-kappa-B activation and apoptosis.	rs11634397	Not associated	2014 [17]
AP3S2	Original research (genotyping)	15	It facilitates the budding of vesicles from the Golgi membrane and may be directly involved in trafficking to lysosomes.	rs202899	Not associated	2014 [17]
PRC1	Original research (genotyping)	15	This gene encodes a protein that is involved in cytokinesis. Among its related pathways are Cytoskeletal Signaling and Signaling by Rho GTPases.	rs8042680	Not associated	2014 [17]
FTO	Original research (genotyping)	16	Indicate a role in nervous and cardiovascular systems and a strong association with body mass index, obesity risk, and type 2 diabetes	rs11642841 rs9939609	Not associated Not associated	2014 [17] 2014 [21]

(Continued)

Tested gene	Type of study	Chromosome location	Gene function	Risk allele	Association with T2D	Year and Reference
HNF1B	Original research (genotyping)	17	The gene has been shown to function in nephron development, and regulates development of the embryonic pancreas.	rs4430796	Not associated	2014 [17]
UBE2E2	Original research (PCR-RFLP)	3	Involved in ligase activity and acid-amino acid ligase activity.	rs7612463	Not associated	2014 [20]
MC4R	Original research (genotyping)	18	Plays a central role in energy homeostasis and somatic growth.	rs17782313 rs12970134	Not associated Not associated	2014 [21] 2014 [21]

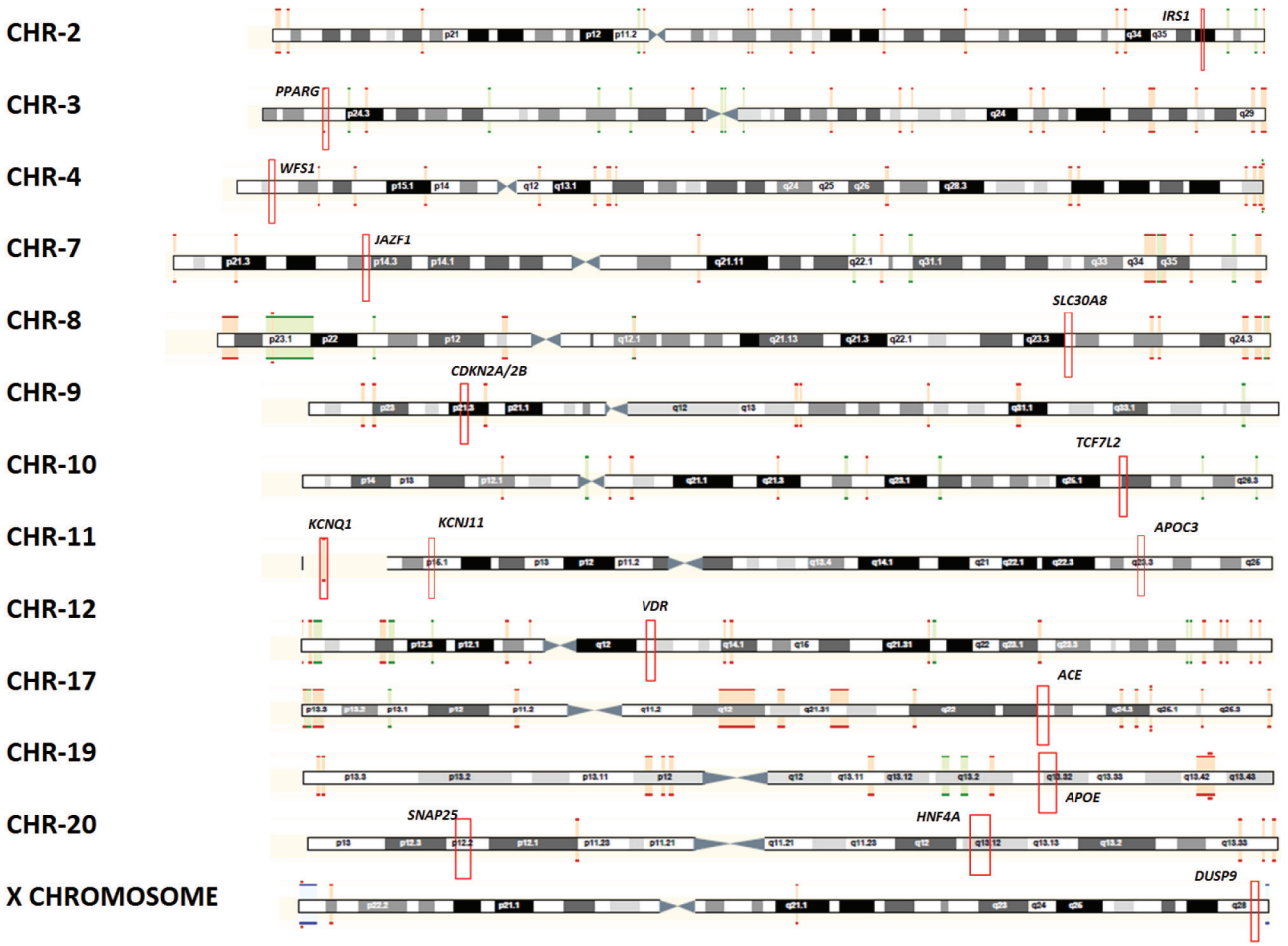

Figure 2. *Chromosomal mapping of genes carrying T2D associated SNPs reported in the Saudi population generated using Ensembl release 90—August 2017 © EMBL-EBI.*

Discussion

Our review provides an integrated perspective of studies published on the genetics of T2D in the Saudi population. The analyzed studies identified 23 polymorphisms in 17 genes that are strongly associated with T2D risk in people of Saudi ethnicity. The studies largely used genotyping technology with modest sample sizes to find genetic variants associated with T2D risk. T2D is a complex disease in which genetic determinants are not solely responsible for disease development; environmental factors also play a crucial role. Earlier genetic studies were limited to genetic factors that showed a strong effect on monogenic conditions on a small number of recruited subjects. However, the last decade has witnessed tremendous advancements in molecular methods that have enabled the detection of genetic variants associated with polygenic and complex diseases. GWAS are usually carried out on large sample groups and are capable of scanning the whole genome (28). GWAS have been conducted in several populations to indicate the genetic risk of diabetes. Previous studies found a

strong association between more than 60 loci and T2D in European and Asian populations (29). In 2017, more than 75 robust associations were reported to be associated with T2D risk considering the total publications around the world (9). A large number of reported genetic variants suggested that multiple genes could influence T2D. However, these loci only explain approximately 10% of T2D heritability (30). Taking into consideration the studies carried out on Saudi ethnicity groups to explore the genetic associations of T2D development, we found 18 studies (10–27) that reported genetic susceptibility to T2D. No studies reported any novel associations and most were candidate genes demonstrated to be associated with T2D in Western populations. Of the 18 publications evaluated, 23 polymorphisms (covering 17 genes) showed a strong association with T2D risk and 44 polymorphisms (covering 37 genes) showed no association with T2D risk. In total, until now, only 23 SNPs were reported to be risk factors for T2D in the Saudi population (Table 1). Failure to replicate the remaining 44 polymorphisms could be due to the small sample sizes used in the studies. Among the collected publications, the subject (i.e., T2D cases) sample size varied between 90 and 2,401 subjects. The study that reported the highest number of samples was Al-Daghri et al. (17), who recruited a relatively large sample size of 2,401 subjects and detected eight associated genetic variants out of 38 tested. As shown in Table 1, all of the observed associations indicated a higher risk of T2D when inheriting the risk allele, except for variants near the *VDR* and *ABCA1* genes, which seem to have a protective effect against T2D (15,16). However, this protective effect of *VDR* contradicts other studies, indicating an increased risk of T2D when inheriting the respective variant (31,32). The 23 polymorphisms studied in the Saudi population increase the risk of diabetes through various mechanisms. Most of the reported genes (Table 1) have a primary or secondary connection with glucose and insulin metabolic pathways. One strength of this systemic review is that it is the first to review the whole spectrum of evidence from the Saudi population regarding the genetic risk of T2D. More importantly, we examined the studies (Table 1) that reported genetic variants that were not associated with T2D risk and were able to demonstrate that the respective variant either showed a protective or had no effect on T2D development in Saudi ethnicity. This study also has limitations. First, for the collected publications, we did not evaluate the core methodological details that include Hardy-Weinberg equilibrium testing and the sample size/power calculation. Second, compared to studies conducted on European populations, the sample sizes in the collected articles were substantially smaller. It is possible that with larger sample sizes and more comprehensive platforms, the previously proposed candidate genes may reach statistical significance.

Conclusion

In summary, we conducted a systematic assessment of the current evidence of genetic determinants of T2D risk in Saudi Arabia. The genetic risk factors identified in this review represent promising T2D susceptibility genes that could be studied in larger-scale to expand our knowledge of the underlying genetic mechanisms of T2D among Saudi ethnicity. In the near future, we could use these findings to design genetic screening tools that could robustly predict T2D, which may provide an opportunity to detect or predict T2D at an early stage.

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The authors declare that there are no conflicts of interest.

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