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Review

Genetics and genomics studies in type 2 diabetes: A brief review of the current scenario in the Arab region

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ABSTRACT

Background: Type 2 diabetes (T2D) is a polygenic and multi-factorial complex disease, the challenge to find genetic markers that could explain the risk of development of this disease still remains unresolved. The Arab region is one among the populations with a high prevalence of T2D and a large number of studies have been carried out in exploring the genetic factors associated with T2D risk.
Aim: To summarize the recent developments in the Arab world based on the recent studies that had looked into genetic factors associated with the development of T2D in the Arab populations.
Methods: A systematic literature search was conducted to identify studies published between 2015 and 2018 reporting genetic factors or polymorphisms associated with the risk of T2D in the Arab world. The online databases PubMed and Web of Science were used to perform the literature search.
Conclusion: The present study has evaluated 14 studies published during the year 2015–2018. Studies from Egypt, Iraq, Jordan, Oman, Qatar, Saudi Arabia, Tunisia, and United Arab Emirates had been explored studying the associations of *GIPR, ADIPOQ, FTO, (GRCh38.p12), MLXIP, AKNAD1, KCNJ11 CDKAL1, CDKN2A/2B, TCF7L2, ACE, SNAP25, ELMO1, VDR, KCTD8, GABRA4 and PRKD1* genes with T2D development.

1. Introduction

Diabetes and its complications remain one of the leading causes of death worldwide. According to the International Diabetes Federation, approximately 425 million people worldwide met the criteria for diabetes in 2017; of these, approximately 50% (~212 million) remain undiagnosed and face a higher risk of developing related complications [1]. Type 2 diabetes (T2D) remains the most prevalent form of diabetes worldwide, and its incidence has increased in parallel with social and cultural advances. Specifically, the Arab world has witnessed a dramatic increase in the prevalence of T2D during the last 30 years. During this time, the Arabian Gulf region has experienced drastic improvements in living standards and rapid urbanization as a result of the income generated from oil-rich resources. However, these improvements have also led to drastic changes in the dietary habits of people in this region, as well as reductions in physical activity and increases in sedentary lifestyle habits [2,3]. In the Arab world, the highest prevalence of diabetes in adults was reported in Saudi Arabia (18.5%), whereas the lowest prevalence was reported in Mauritania (2%), according to the International Diabetes Federation in 2017 [1]. Currently, six Arabic-speaking countries are considered global leaders in terms of the prevalence of T2D, namely Kuwait, Lebanon, Qatar, Saudi Arabia, Bahrain, and United Arab Emirates (UAE) [1,2].

In recent years tremendous changes had occurred in the field of molecular genetics and personalized medicine especially on exploring novel genetic factors associated with complex diseases like T2D with the advancement of new and improved genetic techniques including the next generation sequencing (NGS). In this review, we summarize recent developments from studies on the genetic factors associated with the development of T2D in the Arab world published between 2015 and 2018, which were based on the latest available genetic technologies. Few such studies have been conducted in this region of the world. Therefore, our study will provide valuable contributions to advanced genetic research and a personalized approach to diabetes management.

2. The high prevalence of diabetes mellitus in the Arab world

The diabetes epidemic has expanded significantly in the last two decades, and the increasing prevalence of T2D is now a major

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Table 1
Genes studied during the period 2015–2018 in the Arab population.

Genes	Major Function	Chromosome	SNP studied	Country	Study and year
GIPR	Encodes a G-protein coupled receptor for gastric inhibitory polypeptide (GIP).	19	rs2302382	Egypt	Shalaby, 2017 [11]
ADIPOQ	Important adipokine involved in the control of fat metabolism and insulin sensitivity, with direct anti-diabetic, anti-atherogenic and anti-inflammatory activities.	3	rs2241766	Iraq	Hussain, 2018 [12]
			rs266729	Iraq	Kaftan, 2015 [13]
FTO	Plays an important a role in nervous and cardiovascular systems and a strong association with body mass index, obesity risk, and type 2 diabetes.	16	rs9939609	Iraq	Younus, 2017 [14]
			rs17817449	Iraq	Younus, 2017 [14]
chr20:10771962 (GRCh38.p12)	–	20	rs6134031	Jordan	Dajani, 2017 [15]
MLXIP	Among its related pathways are Insulin resistance and Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	12	rs4758690	Jordan	Dajani, 2017 [15]
AKNAD1	This gene encodes a protein which contains a domain found in an AT-hook-containing transcription factor.	1	CNV chr1:109367944-109371874	Jordan	Dajani, 2017 [15]
TCF7L2	The protein has been implicated in blood glucose homeostasis. Genetic variants of this gene are associated with increased risk of T2D.	10	rs7903146	Oman	Al-Sinini, 2015 [16]
			rs7903146	Qatar	O'Beirne, 2016 [5]
			rs4506565	Qatar	O'Beirne, 2016 [5]
			rs12255372	Saudi Arabia	Acharya, 2015 [17]
			rs4506565	Saudi Arabia	Acharya, 2015 [17]
			rs10885409	UAE	Al-Safar, 2015 [21]
KCNJ11	The protein encoded by this gene is an integral membrane protein and inward-rectifier type potassium channel.	11	rs5219	Oman	Al-Sinini, 2015 [16]
CDKAL1	The protein encoded by this gene is a member of the methylthiotransferase family. GWAS have linked single nucleotide polymorphisms in an intron of this gene with susceptibility to T2D.	6	rs10946398	Oman	Al-Sinini, 2015 [16]
CDKN2A/2B	Involved in cyclin-dependent protein kinase inhibitor activity; and tumor suppression.	9	rs10811661	Oman	Al-Sinini, 2015 [16]
ACE	This gene encodes an enzyme involved in catalyzing the conversion of angiotensin I into a physiologically active peptide angiotensin II.	17	Insertion/deletion	Saudi Arabia	Al-Saikhan, 2017 [18]
SNAP25	The gene product for this gene is a presynaptic plasma membrane protein involved in the regulation of neurotransmitter release.	20	rs363050	Saudi Arabia	Al Dhaghri, 2016 [19]
ELMO1	Increased expression of this gene and dedicator of cytokinesis 1 may promote glioma cell invasion, and single nucleotide polymorphisms in this gene may be associated with diabetic nephropathy	7	rs7782979	Tunisia	Turki,2017 [20]
			rs10255208	Tunisia	Turki,2017 [20]
VDR	This gene encodes vitamin D3 receptor. This receptor also functions as a receptor for the secondary bile acid, lithocholic acid.	12	rs1544410	UAE	Al-Safar, 2015 [22]
			rs2228570	UAE	Al-Safar, 2015 [22]
KCTD8	Among its related pathways are Sweet Taste Signaling and Neuropathic Pain-Signaling in Dorsal Horn Neurons.	4	rs4695718	UAE	Al-Safar, 2015 [22]
GABRA4	Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain where it acts at GABA-A receptors, which are ligand-gated chloride channels.	4	rs2055942	UAE	Al-Safar, 2015 [23]
PRKD1	The protein encoded by this gene is a serine/threonine protein kinase involved in many cellular processes, including Golgi body membrane integrity and transport, cell migration and differentiation, MAPK8/JNK1 and Ras pathway signaling, MAPK1/3 (ERK1/2) pathway signaling, cell survival, and regulation of cell shape and adhesion.	14	rs1953722	UAE	Al-Safar, 2015 [23]

Gene function data are taken from Ref. [24].

health-related challenge faced by both developed and developing countries. Despite the global nature of this crisis, the Arab region stands out due to the predicted 96.2% increase in the prevalence of diabetes by 2035 [1]. According to the International Diabetes Federation in 2017, the prevalence of diabetes in adults among the Arab countries are as follows: Saudi Arabia (18.5%), Bahrain (16.2%), United Arab Emirates (15.6%), Egypt (15.2%), Kuwait (15.1%), Lebanon (14.6%), Qatar (14.1%), Djibouti (12.7%), Libya (11.2%),Sudan (10.9%),Oman (10.7%), Tunisia (9.8%), Jordan (9.5%), The Comoros Islands (7.7%), Iraq (7.5%), Morocco (7.3%), Syria (7.1%), Palestine (7%), Algeria (6.9%), Somalia (4.5%),Yemen (3.8%) and Mauritania (2) [1]. Both environmental and genetic risk factors have been identified as crucial factors in the development of T2D. Of these, the rapid increase in the rate of T2D specifically in the Arab region has been exacerbated by the high rate of consanguineous marriages, obesity, rapid urbanization and a lack of exercise. Despite these unique factors, there is a paucity of available literature from the Arab region. A study published by Siddiqui et al. [4] in 2015 provided a detailed review of the genetic variations predisposing individuals to T2D identified via genome-wide association studies, as well as a perspective on diabetes in the Arab population.

3. The current scenario and genetic studies in the Arab world

Regardless of notable advances in the fields of molecular genetics and sequencing, the majority of genetic studies of T2D have been conducted in adult populations of European descent, which has a general T2D prevalence of 2.4–14.7% [5]. Excluding few studies of specific candidate genes, relatively little attention has been directed toward the genetic risk factors associated with Middle Eastern populations, with an estimated prevalence of 6–23.9% in adults [5]. However, the period of 2015–2018 witnessed significant developments in genetic research in the Arab world. Of the 14 genetic studies published during this period, the very recently published study by Rubeaan et al. [6], which involved design of "Arab Diabetes Gene-Centric Array (ADGCA)" custom array chip targeting the Arab population, and a 2016 study by Beirne et al. [5], which evaluated T2D risk allele loci in the Qatari population, are the best evidences for genetic studies that have explored a large sample size [5] or attempted to design a novel genetic screening tool for the Arab world [6].

4. Recent studies and T2D genes in the Arab population/ results

In this study, we reviewed the latest genetic studies on T2D in the Arab population, which were published between 2015 and 2018 (Table 1). We conducted a systematic literature search using the online databases PubMed and Web of Science to identify recent publications reporting genetic factors or polymorphisms associated with the risk of T2D in the Arab world. The genetic studies published during 2015–2018 on T2D covered studies from Iraq, Jordan, Oman, Qatar, Saudi Arabia, Tunisia, and United Arab Emirates and explored the associations of *GIPR, ADIPOQ, FTO, (GRCh38.p12), MLXIP, AKNAD1, KCNJ11 CDKAL1, CDKN2A/2B, TCF7L2, ACE, SNAP25, ELMO1, VDR, KCTD8, GABRA4 and PRKD1* with T2D development [11–23]. *TCF7L2,* located on chromosome 10, was the most commonly studied gene in relation to T2D in the Arab population. A previous meta-analysis study had looked into the genetic factors associated with the risk of T2D in both Arab and Caucasian ethnicities considering studies published till March 2011 and found that *TCF7L2* (rs7903146), *KCNJ11* (rs5219), *ACE I/D* and *MTHFR* C677T polymorphisms were significantly associated with T2D in the Arab population.

5. Conclusion

Recent genetic studies have identified about 140 loci that affect the risk of T2D [7–10], and future studies are expected to yield many more genetic determinants of T2D. One among the recent studies, published in Nature Genetics [10] explored the loci most frequently associated with T2D in 898,130 individuals and was one of the largest studies of its type. By contrast, although a few of the genes included in this study [10] (*GIPR, FTO, KCNJ11 CDKAL1, CDKN2A/2B, TCF7L2, ACE*) were also examined in the Arab population [5,11–23], studies from the Arab world remained limited to candidate genes and smaller sample sizes. Again, this discrepancy highlights the great need for collaborative research in the Arab world. This approach would enable interactions between research centers and populations worldwide, thus providing better access to comparable samples, improved technologies, and more accurate and conclusive results. The Saudi genome program (https://www.saudigenomeprogram.org/en/) and Qatar genome program (https://qatargenome.org.qa/) are the existing two very promising initiatives that aims to position the Arab world among the countries considered pioneers in the implementation of genetic screening and precision medicine. Such projects also could play a pivotal role in elucidating the unknown causal factors for complex diseases like T2D. These developments in the Arab world would certainly facilitate research breakthroughs and advances in disease diagnosis and enable strategies for future healthcare planning.

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Consent of patients

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Ethical approval

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Declaration of conflicting interests

The authors declare that there is no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.017.

List of abbreviations

T2D	Type 2 Diabetes
UAE	United Arab Emirates

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