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Evaluation of SLC16A11 Gene Polymorphisms in Type 2 Diabetes Mellitus Patients

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Abstract

The most prevalent form of diabetes, type 2 diabetes mellitus (T2DM), is defined by hyperglycemia in the presence of hyperinsulinemia, which is brought on by insulin resistance and β-cell functional abnormalities of insulin secretion. The work aims to study the association of the SLC16A11 gene with T2DM; besides the 50 healthy individuals who served as the control group, 50 diabetic patients also had their blood drawn. Participants were divided into two groups based on the following criteria: A control group consists of 50 healthy participants between the ages of 20 and 70, while the patient group consists of 50 participants who were diagnosed with diabetes. The patient group had 58% male and 42% female participants, whereas the control group had 52% male and 48% female participants. Despite the fact that many genetic discoveries are relatively recent and have not yet had a significant impact on our understanding of the pathogenesis of diabetes, they have already made a substantial contribution by revealing pathways that could not have been connected to diabetes by presumptive models that already exist. Nevertheless, it's critical to remember that diabetes is probably a far more complex condition than the distinction between T1DM and T2DM suggests.

Keywords: SLC16A11, type 1 diabetes mellitus, typs 2 diabetes mellitus, polymerase chain reaction.

1. Introduction

Diabetes mellitus (DM), sometimes known as diabetes, is a set of metabolic illnesses characterized by excessive blood sugar levels [1]. According to the World Health Organization (WHO, 2021), DM is a chronic condition that occurs when the body either produces inadequate quantities of insulin or is unable to use insulin effectively. Diabetes affects metabolism by reducing glucose levels or impairing the body's ability to regulate blood sugar levels owing to inadequate insulin secretion or activity. Amino acids, or carbohydrates, can be used to make triglycerides and fatty acids.

Due to non-diabetic cells' failure to identify blood glucose absorption, enzymes in the pentose phosphate, glycolytic, and lipogenic pathways (PPP) are blocked, with increased gluconeogenic, glycogenolytic, and lipolytic activity [2]. The most common form of diabetes is type 2 diabetes (T2DM), called non-insulin-dependent diabetes mellitus or "adult-onset" diabetes, so-called because it typically develops in adults over age 35. However, it can develop at any age [3]. T2DM is caused by islet cell dysfunction, which is caused by a combination of two primary factors: the failure of insulin-sensitive organs to respond to insulin and defective insulin production by pancreatic islet cells. A persistent dysregulation of the hyperglycemia state caused by an insufficient compensatory insulin secretory system may increase the risk of heart, vasculature, eyes, kidneys, and nerve diseases [4]. Genetic and environmental factors can contribute to the clinical picture of T2DM [5]. Changes in specific substrates of particular proteins and transports, such as the 14-membered monocarboxylate transporter (MCT) family, which is defined by two highly conserved sequences, can play vital roles in most cellular functions in the pathophysiology of diabetes and cancer [6]. Members of that family include MCT1 (SLC16A1), MCT4 (SLC16A3), and MCT11 (SLC16A11). Despite their structural similarity, members of the SLC16 family mediate the transport of various substances through two separate active methods based on their function. SLC16A11 can be expressed in a small amount of human tissue, whereas the highest levels can be found in the thyroid, liver, and salivary glands. It is a member of the first class of SLC16 participants (Category I: MCT1 and MCT4), which use a proton (H+)-coupled mechanism to transport essential monocarboxylic acids, including lactate, pyruvate, and ketone bodies.

Additionally, MCT11 may function as a monocarboxylate transporter linked to the proton [7]. A positive genetic correlation between T2DM and DNA polymorphisms was observed in the SLC16A11 coding area. It is debatable, nonetheless, how these T2DM variations impact SLC16A11's functionality [8]. Solute carrier (SLC) 16A11 has been identified as a T2DM risk gene. SLC16A11's physiological role has not yet been determined. However, how these SLC16A11 variants affect people with T2DM remains unknown. The blood lipids were particularly impacted by the SLC16A11 genotype when it came to T2DM laboratory parameter values. Lipid metabolism may be involved in SLC16A11's function [9]. This study was designed to look at the relationship between the SLC16A11 gene and T2DM.

2. Materials and Methods

2.1 Study design

In this study, it has been selected two groups of participants. The first group includes T2DM patients, and the control group comprises healthy people. The current work was completed in the Biochemistry Department lab at the College of Sciences, University of Baghdad. It was intended for sample collection to happen between September 2021 and January 2022.

Patients group; at the Diabetes and Endocrinology Center in Baghdad, Iraq, 50 individuals with T2DM were hospitalized.

The control group consisted of 50 people who appeared to be in good health. Both the patient and control groups included members of the same ethnic group.

2.2 Exclusion criteria

T1DM, diabetes with a duration of > 20 and 5, age > 60 and 40, smoking, renal failure, thyroid illness, malignant disease, hepatic disease, pregnant women, and medications with a proven effect on bone metabolism such as anticonvulsants, heparin sodium, and corticosteroids, were excluded.

2.3 Definition of diabetic status

According to the American Diabetes Association (ADA) [10], for people with diabetes, the range for the hemoglobin A1C (HbA1C) level is below 6.5%. These people have a fasting glucose test below 126 mg/dL or 200 mg/dL after fasting for at least eight hours. For people without diabetes, the normal range for the HbA1C level is below 5.6%, with a fasting length of more than eight hours. These people have a fasting glucose test below 100 mg/dL and post-OGTT glucose levels under 140 mg/dL. The statistical analysis didn't include people with pre-diabetes intermediate phenotypes. Because at least one diabetic autoantibody characterizes T1DM, which is primarily an autoimmune condition (glutamic acid decarboxylase or insulinoma-associated antibody) [11]; however, in the current literature, these measures have not been investigated in HCHS/SOL. For the sample employed in the same study, we were unable to distinguish T2DM from T1DM. Furthermore, research indicates that the age at which T2DM initially appears has lately fallen significantly, making it impossible to differentiate between different forms of diabetes based on diagnosis age. In any event, given that only one of these sample's 20–70-year-old participants could potentially have T1DM based on the use of insulin and that they were all included in our HCHS/SOL sample, it doesn't seem likely that removing T1DM and T2DM will have a significant impact on the results.

2.4 Methods

When it is necessary to boost the sensitivity and specificity of PCR, such as when amplifying a particular member of a polymorphic gene family or when creating a cDNA copy of an mRNA present at extremely low abundance in clinical material containing DNA, polymerase chain reaction (PCR) is performed, Agarose Gel Electrophoresis was used to assess the DNA's concentration and purity. In PCR, two separate amplification procedures using a unique pair of primers are usually performed. For the second PCR, which is primed by oligonucleotides placed between the primers of the first PCR, the product of the first amplification reaction acts as the template. Using two sets of oligonucleotides increases the PCR's sensitivity because more cycles may be done. The specificity of the response has been improved by the binding of two distinct sets of primers to the same target template. While nested PCR is a valuable method for amplifying sections of long templates, it requires knowledge of the target sequence. Hot start PCR should be performed on the tubes or microtiter plate after placing them in the thermal cycler.

For the initial round of amplification, use the denaturation, annealing, and polymerization durations and temperatures listed in the following **Table 1**.

Table 1. The PCR cycling program.

Steps	Temp. (°C)	Time	Cycle
Initial Denaturation	95	3 min	1
DNA Denaturation	95	30 sec	35
Annealing	51	45 sec	35
Extension	72	30 sec	35
Final extension	72	7 min	1

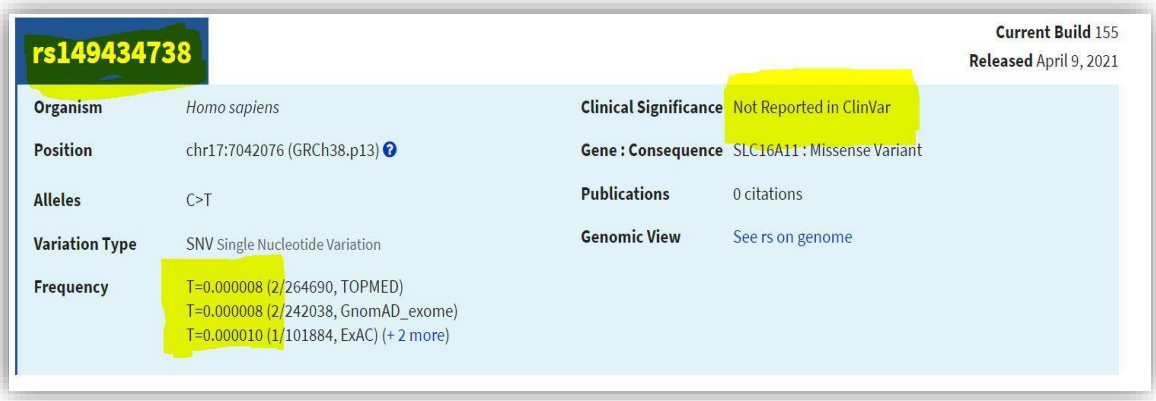
3. Results

This result is explained by the fact that this mutation is rare in the population. So, no mutation appeared in 100 Iraqi (50 patients and 50 controls). The frequency of the SNP is C=0.00004 (1/248500, Gnomed_exome), as shown in **Table 2**.

Table 2. The Rs 747934148.

The explanation for this result is that this mutation is rare in the population. So, no mutation appears in 100 Iraqis (50 patients and 50 control). The frequency of the SNP is C= 0.00008 (2/242038, Gnomed_exome), as shown in **Table 3**.

Table 3. The Rs149434738.



This result is explained by the fact that this mutation is rare in the population. So, no mutation appeared in 120 Iraqis (50 patients and 50 controls). The frequency of the SNP is C=0.00008(2/242038, Gnomed_exome), as shown in **Table 4**.

Table 4. The Rs767615781.

4. Discussion

Diabetes is a chronic health condition that affects how the body is unable to maintain glucose homeostasis through adequate absorption. T1DM and T2DM are the two categories into which diabetes has historically been categorized. Both types of diabetes can lead to chronically high blood sugar levels. That increases the risk of diabetes complications. Over the past few decades, the knowledge of diabetes has expanded to incorporate the potential that a number of overlapping environmental and inherited factors may contribute to various disease presentations. Though they are two distinct conditions, T1DM and T2DM represent the two ends of a diabetic spectrum. There are several subgroups in the intermediates, including maturity-onset diabetes in the young (MODY) and latent autoimmune diabetes in adulthood (LADA). T1DM, commonly referred to as juvenile diabetes or insulin-dependent diabetes, is caused by the autoimmune destruction of pancreatic beta cells. Due to the existence of autoantibodies, particularly antibodies against glutamic acid decarboxylase, insulin injections are necessary (GAD). Children, teenagers, and young adults under the age of 35 are most frequently diagnosed with it. Numerous variables, such as geography, age, gender, and family history, have an impact on the development of T1DM [12]. Ostrow et al. noted that. Only 10% to 15% of people with new diagnoses had a T1DM relative [13].

The average prevalence risk for children without a family history of T1DM is 0.4%; however, this risk increases to 6% and >30% when both parents are affected, respectively. While dizygotic twins had an 8% recurrence risk, monozygotic twins had a 50% recurrence risk with a 10% possibility within 10 years after the first twin's diagnosis [14,15].

MODY's diagnosis is crucial for both the patient and the family. The study estimates that the risk is just about 2%–4% for children of afflicted mothers and as high as 5%–8% for children of affected fathers [19–20]. Siblings are expected to have a 15 percent relative risk of T1DM. Increasing evidence suggests that genetic, epigenetic, and environmental variables might play a critical role in the T1DM disease process [16].

The heritability of T1DM can be attributed to genetic studies in 80% of cases [17]. The class II alleles of HLA account for over 50% of a person's genetic susceptibility to the condition, and non-HLA loci such as the interleukin 2 receptor (IL2RA), CTLA4, PTPN22,

the insulin gene, and others are now the most significant susceptibility genes for T1DM [18].

Viruses from the picoRNA family manifest before autoantibodies and are more common in newly diagnosed T1DM patients than in the general population. Environmental contaminants, vitamin D exposure, and disorders in the gut flora have been considered ecological variables in the past [19-21]. The type of diabetes known as LADA (Latent Autoimmune Diabetes in Adults) affects about 7% of all diabetic patients in Europe. For the first six months following diagnosis, LADA is often referred to as diabetes with GAD antibody positivity that appears after the age of 35 and does not require insulin [22–25]. A threshold that causes T1DM also causes GAD-AB positivity. As a result, on the left side of the spectrum, high-ab titer LADA is comparable to type 1 diabetes, while LADA with smaller titers is similar to T2DM [26]. However, all types of diabetes present a significant risk factor for LADA [27].

The monogenic form of diabetes known as MODY (Maturity-Onset-Diabetes of the Young) has more than 10 different genes with well-detected mutations, and this number is steadily rising. Transmission of early-onset autosomal dominant diseases (25 years) The characteristics of the condition are hyperglycemia and varying degrees of β-cell dysfunction [28]. Contrary to widespread assumption, the MODY genes—HNF1A, HNF4A, HNF1B, GCK, and PDX1—are not associated with a variety of diseases. The majority of MODY mutations are different due to the high allelic diversity of the MODY gene; so far, the GCK (MODY2) and HNF1A (MODY3) genes have more than 200 mutations found in them [29, 30]. Sequencing is necessary for an accurate MODY diagnosis. The development of next-generation sequencing technologies has dramatically increased the likelihood of a correct MODY diagnosis. Maternally inherited diabetes and deafness (MIDD) are caused by the A3242G mutation in mitochondrial DNA (mtDNA) [30,31]. Because mtDNA can only be passed from mother to child, MIDD serves as an example of maternal transmission. MELAS syndrome, which is also brought on by the same mutation in mtDNA, is characterized by neurological issues along with hearing loss. Stroke, lactic acidosis, mitochondrial myopathy, and encephalopathy are other symptoms of MELAS syndrome. Neonatal diabetes can manifest at birth or within the first six months of life in both temporary and chronic types [32]. The primary kind of treatment for neonatal diabetes has been linked to abnormalities in a range of genes and requires an accurate genetic diagnosis (KCJN11, SUR1, GCK, INS, etc.). In addition to severe diabetes, people with KCJN11 gene mutations also have developmental issues. These symptoms appear to be better when high-dose sulfonylurea therapy is substituted for insulin treatment [33]. A transient type of diabetes called gestational diabetes mellitus (GDM) occurs during pregnancy as hyperglycemia, which obviously doesn't have diabetes and disappears after delivery. An estimated sibling risk ratio of 1.75 was reported for GDM [34, 35], despite the fact that changes to the diagnostic criteria made it more challenging to identify GDM patients in the past and determine heredity accurately. It may help to explain why women with a history of GDM are more likely to develop T2DM [36, 37] and that some GDM-associated polymorphisms and T2D risk variants have been found to overlap [38,39]. Women with GDM are more likely to experience macrosomia in neonates, fetal

hyperinsulinism, and unfavorable pregnancy outcomes despite the fact that these conditions are temporary [40, 41].

Due to the recent rapid breakthroughs in technology, this will be possible in the not-too-distant future. Despite recent advancements in genetic discoveries, they haven't yet had a significant impact on our understanding of the pathogenesis of diabetes. They, however, have already made a substantial contribution by revealing pathways that could not have been connected to diabetes by presumptive models that already exist. Nevertheless, it's critical to remember that diabetes is probably a far more complex condition than the distinction between T1DM and T2DM suggests. The more exact division into subgroups might accelerate genetic investigation into T2DM and open the door to more customized therapy. It will also be necessary to use a thorough systems biology approach to understand how genetic diversity influences diabetes entirely. This will be attainable in the not-too-distant future because of the recent rapid advancements in technology [42].

5. Conclusion

Numerous genetic variations linked to T2DM have made significant advances in learning more about genetic science. The total heritability of diabetes has so far only partially been explained by the genetic landscape of T2DM susceptibility. Numerous genetic investigations, family sequencing, and meta-analyses have all become effective methods for comprehending the etiological architecture of T2DM. Even though many genetic discoveries are relatively recent and have not yet made a significant impact on our comprehension of the pathogenesis of diabetes, they have already contributed significantly by revealing pathways that could not have been linked to diabetes by presumptive models that already exist. The ability to classify patients into subgroups based on the genetics of T2DM could facilitate research data. A thorough biology-systems approach is also necessary for developing clinical guidelines on how genetic diversity influences diabetes.

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Conflict of Interest

There is no conflict of interest.

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Ethical Clearance

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