33 (2022) 201064

Contents lists available at ScienceDirect

Human Gene

journal homepage: www.journals.elsevier.com/human-gene

Evaluation of possible association of interferon-induced helicase (*IFIH1*) gene polymorphism with type one diabetes mellitus in a sample of Iraqi children

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ARTICLE INFO

Keywords:
Type 1 diabetes
Interferon induced helicase 1
Polymorphism

ABSTRACT

Diabetes of type 1 is a chronic autoimmune disease that results in the progressive and modest loss of pancreatic cells over the course of the disease's lifetime.T1D may have a hereditary and environmental component. The purpose of this study was to found any association between the *IFIH1* rs1990760 polymorphism and T1D in Iraqi children. There were 75 children with type 1 diabetes participated in this study between January and March of 2021. RBS, serum fructosamine, HbA1c and pancreatic beta cell autoantibodies were estimated in all samples. Three SNPs in *IFIH1* gene polymorphisms (rs35667974, rs35732034 and rs1990760) were investigated for their association with the development of T1D. SNP of rs1990760 had three genotypes in patients and controls (GG, GA, AA). The wild type GG genotype was more frequent in controls than patients (32% vs. 22.67%), while the mutant genotype (AA) was more frequent in patients (30.66%) than controls (22.67%) with no significant difference in both. The study was revealed *IFIH1* polymorphism not associated with T1D in Iraqi children.

1. Introduction

Diabetic mellitus is a combination of the words diabetes and mellitus, which are derived from the Greek word diabetes, which means "siphon-to-pass-through." Researchers believe that Apollonius of Memphis, who lived circa 250–300 BCE, was the first person to use the term "diabetes." As a result of this finding, the ancient Greek, Indian, and Egyptian civilizations established the word Diabetes Mellitus, which means "diabetic diabetes." In 1889, Mering and Minkowski discovered that the pancreas plays a role in the development of diabetes and published their findings in Diabetes (Sapra et al., 2021). Diabetes mellitus (DM) is a long-term metabolic condition that damages the heart, blood vessels, eyes, kidneys, and nerves by causing increased blood glucose levels (Kononenko et al., 2020).

Diabetes is one of the most rapidly expanding worldwide health crises of the twenty-first century, according to data from national health surveys and World Health Organization (WHO) reports. According to current estimates, the number of diabetics will rise to 643 million by 2030 and 783 million by 2045. A total of 541 million individuals are predicted to suffer from poor glucose tolerance by 2021. Diabetes-related deaths are expected to claim the lives of approximately 6.7 million persons between the ages of 20 and 79 worldwide by the year 2021. Every year, the number of children and adolescents (i.e., those ages 12 to 19) who have diabetes grows. In 2021, >1.2 million children and adolescents will suffer from type 1 diabetes, according to estimates. Diabetes-related health care costs have already exceeded one trillion dollars and are expected to do so by 2030 (SUN, Hong et al, 2022). Age > 60, dyslipidemia, pre-diabetes, insulin resistance, hypertension, obesity, family history of diabetes, and poor education level were the most strongly related risk factors for diabetes mellitus (Urrutia et al., 2021).

As a result of its complicated pathophysiology and diverse appearance, diabetes mellitus (DM) is difficult to classify. Because of this, diabetes can be subdivided into two basic forms or categories: type 1 diabetes and type 2 diabetes (Sapra et al., 2021). Diabetic type 1 diabetes, also known as insulin-dependent diabetes mellitus (IDDM),

Abbreviations: T1D, Type 1 diabetes; IFIH1, Interferon induced helicase 1; BMI, Body mass index; RBG, Random blood glucose; HbA1C, Hemoglobin A1C; ICA, Islet Cells Antibody; Anti-IA2, Anti-Islet Antigen Antibody; GADA 65, Glutamic Acid Decarboxylase Antibodies..

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https://doi.org/10.1016/j.humgen.2022.201064
Received 18 February 2022; Received in revised form 24 April 2022; Accepted 1 June 2022
Available online 6 June 2022

juvenile-onset diabetes, or insulin-dependent diabetes mellitus (IDDM), accounts for around 5–10% of all diabetes cases. Hyperglycemia is the result of an autoimmune illness characterized by T lymphocyte-mediated death of pancreatic beta cells, which culminates in insulin deficiency and, eventually, hyperglycemia (Banday et al., 2020). However, despite the fact that the pathogenesis of this autoimmune disease is still not fully understood, it has been revealed to be influenced by both genetic and environmental factors. It is common for this pancreatic β-cell-specific autoimmunity and the illness itself to develop quickly in most cases, as observed in newborns (juvenile onset), or it may develop gradually, as seen in adults (late onset)(Kahaly and Hansen, 2016).

This disease's prognosis is frequently determined by the variety in the rate at which the immune-mediated death of pancreatic β-cells occurs over time. In certain cases, particularly in children and adolescents, beta-cell breakdown and subsequent failure occur rapidly, resulting in diabetic ketoacidosis (DKA), which is frequently referred to as the disease's earliest manifestation. Others experience a very slow progression of the disease with only a mild increase in fasting blood glucose levels, which progresses to a severe hyperglycemic state with or without ketoacidosis only in the presence of physiological stress conditions such as severe infections or the onset of other diseases (Banday et al., 2020).

Type 1 diabetes mellitus is an autoimmune disease, and as such, a number of immunological markers, such as autoantibodies, are present. It is thought that the immune-mediated cell death that characterizes this illness is linked to these autoantibodies. Many different types of autoantibodies have been discovered, including antibodies to glutamic acid decarboxylase (GAD65), β-cell cytoplasmic protein autoantibodies (ICAs), antibodies to the tyrosine phosphatases IA-2 and IA-2, insulin autoantibodies (IAAs), and autoantibodies to the islet-specific zinc transporter isoform 8 (IAAs) (ZnT8). Some of these autoantibodies are useful for clinical diagnosis, but in about 85–90% of people with new-onset type 1 diabetes, more of these immunological markers have been detected (Kahaly and Hansen, 2016). Other autoimmune disorders, such as myasthenia gravis (a primary adrenal disorder), Addison's disease (a primary adrenal insufficiency), celiac sprue (a gluten-related disease), pernicious anemia, vitiligo, Hashimoto's thyroiditis, Graves' disease, dermatomyositis, and autoimmune gastritis, are more common in patients with T1DM (Hughes et al., 2016).

Type 1 diabetes has a strong autoimmune component because of its strong connection to the human leukocyte antigen (HLA), its linkage to the *DQA* and *DQB* genes, and its direct effect on the *DRB* genes. Immunological reactions, including autoimmunity, have been reported in these gene regions. Genome-wide association studies have identified a robust connection between this condition and the HLA-DR3 and HLA-DR4 haplotypes. One of the various HLA haplotypes that can raise or decrease a person's susceptibility to type 1 diabetes (Banday et al., 2020). The risk of developing this disease is influenced by many genes and gene regions that are not part of the HLA system. A location known as chromosome 11p5.5, where the insulin gene (*INS*) is located, is among the most prominent of these regions. Tandem-repeated sequences in this gene area have been demonstrated to have an effect on the likelihood of developing this disease. Cytotoxic T lymphocyte antigen 4 *CTLA-4*, Protein tyrosine phosphatase non-receptor type 22 (*PTPN 22)*, Interferon-induced helicase 1 (IFNH1), and cluster of differentiation 25*(CD25)* are non-HLA genes associated with type 1 diabetes (Kahaly and Hansen, 2016).

The etiology of diabetes type 1 (T1D) is currently being investigated in its entirety. Environmental and genetic factors are both well-known to have a role in the onset of the illness; nevertheless, these aspects are still not fully recognized as contributing factors (Roep et al., 2021). People attribute the development of type 1 diabetes to exposure to infections, particularly viral infections (Esposito et al., 2019). It is thought that the viral recognition receptor interferon induced helicase 1 (*IFIH1*), which is located in the cytosol of cells, may play a role in the interaction between genetics and the environment. In the coding region of the *IFIH1* gene, a variety of single-nucleotide polymorphisms have been found; the rs1990760 (A > G, Ala946Thr) variation was the most often detected, with the G minor allele providing a small protection against type 1 diabetes(Blum and Tse, 2020).

People with the G allele have a lower risk of getting type 1 diabetes than those with the A allele, according to prior research in communities with high prevalence of diabetes in Finland and medium prevalence in Hungary (odds ratio 0.81 with 95% confidence interval CI of 0.71–0.92). Those who have the minor G allele, particularly in the Caucasian population, have been shown to have some protection against T1D by studies linking the IFIH1 rs1990760 polymorphism and T1D (Jermendy et al., 2018).

It is undeniable that the genetic architecture of T1D is complicated, and additional gene variations may contribute to the onset of diabetes. T1D onset's seasonal variance offers an intriguing insight to viral impacts and the interaction between genes and the environment (Nyaga et al., 2018). Patients with illnesses that start in the summer or winter should have distinct distributions of disease-predisposing *IFIH1* genetic variations, according to theory, since the environmental pressure from viral infections is so varied in the summer and winter. *IFIH1* rs1990760 polymorphism has not yet been linked to seasonal fluctuation in the clinical onset of T1D, however this has not been ruled out (Jermendy et al., 2018).

Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for around 90–95% of all cases of diabetes, according to the old nomenclature. Insulin-related abnormalities are the primary distinguishing feature of type 2 diabetes. Diabetic symptoms include insulin resistance and beta-cell malfunction (Banday et al., 2020). Insulin resistance occurs when cells in peripheral tissues such as muscle, liver, and fat are less responsive or sensitive to insulin than they should be. Insulin resistance is characterized by decreased insulin sensitivity or responsiveness (Galicia-Garcia et al., 2020). Insulin secretion is increased to compensate for decreased insulin sensitivity in the early stages of the disease, which causes β-cell hyperfunction. Hypoglycemia is prevented by high insulin levels (hyperglycemia) in the bloodstream. A steady loss in insulin sensitivity cannot be offset by an increase in beta-cell insulin production. Insulin insufficiency eventually results from decreased β-cell function and beta-cell malfunction (Esser et al., 2020).

However, several gene regions increase the susceptibility to the T2DM. The most prominent among them are the *miR-143/145* gene (Jahantigh et al., 2021), *LXRβ (NR1H2)* gene (Sargazi et al., 2020b), *HHEX* gene (Galavi et al., 2019), *IGF2BP2* gene (Sargazi et al., 2020a, 2020b), *SLC30A8* gene (Sargazi *et al.,*2020), SREBF-2 gene (Galavi et al., 2018a), *SIRT1* gene (Sadeghi et al., 2021a), and *ADRB-1* gene (Galavi et al., 2018b).The study's goal was to see whether the *IFIH1* rs1990760 polymorphism had any connection to T1D in the Iraqi children.

2. Material and methods

2.1. Specimen collection

In this case-control study conducted from January to March 2021, a total of 75 children were identified with T1D (as patients group) at the Thi-Qar governorate diabetic and endocrine glands center. In addition, left-over blood samples were collected from 75 non-diabetic children who seemed healthy and had no family history of T1D who visited Bint Al-Huda Children's Hospital (as control samples). They comprised boys and girls of the same age as the patients (ranging from one month to 15 years). The ethical approval of the research project was provided by the Institutional Review Board (IRB) at Al-Nahrain University on 10th January 2021 (No. 202011136). Data related to T1D patients was collected, including the distribution of the disease based on sex, age, residency, illness duration, treatment by insulin, and family history related to diabetes mellitus. The body mass index (BMI) was computed as weight (in kg) divided by height square (m^2).

2.2. Biochemical tests and autoantibodies related to T1D

The diagnosis of patients with T1D has been done according to World Health Organization criteria (World Health Organization, 2019) and includes the following biochemical tests: random blood glucose (RBG), hemoglobin A1C (HbA1C), and serum fructosamine. In addition, chemiluminescence immunoassay (CLIA) has been used to detect Islet Cell Antibody (ICA), Anti-Islet Antigen Antibody (anti-IA2) and Glutamic Acid Decarboxylase Antibodies (GADA 65).

2.3. Molecular diagnosis

Blood samples were kept in an ethylene diamine tetra acetic acid tube for DNA extraction. After genomic DNA extraction from 150 samples using the QIAamp DNA Blood Mini Kit (Qiagen, USA), conventional PCR and Sanger sequencing were used to genotype the *IFIH1* SNPs. Three SNPs in *IFIH1* gene polymorphisms (Rs35667974, rs35732034 and Rs1990760) were investigated for their association with the development of T1D. A specific pair of primers were used to amplify the *IFIH1* fragment corresponding to these SNPs.Forward and reverse primer were designed and used as following:

IFIH1-F (5′-TGTAAAACGACGGCCAGTCAAACCTGAAACCACTAACTATTC-3′) and IFIH1-R (5′-CAGGAAACAGCTATGACCTGGCCCACAGCAATTT-3′). PCR was carried out in a 25 μl reaction that included 12.5 μl of Green Master Mix, 1 μl of primers with 10 pmol/μl of each primer, and 2 μl of the DNA template. Nuclease-free water was used to get the volume up to 25 μl in total. Conditions for polymorphism amplification of *IFIH1* in response to temperature cycling are as follows: In this experiment, thirty cycles of denaturation at 94 °C for thirty seconds, annealing at 55°C for thirty seconds, and extension at 72°C for thirty seconds were carried out in this experiment. An additional seven minute extension at 72°C was carried out. Gel electrophoresis of PCR products was done with an expected length of 895 base pairs (bp), Figs. 1 and 2.

2.4. Sanger sequencing

The PCR products were sequenced using the Applied Biosystems 3730XL (ABI3730XL) by Macrogen Company, Korea. The acquired sequences were matched with the normal sequence from Gene Bank using geneious software, and the presence of polymorphisms was determined by comparing the results.

2.5. Statistical analysis

Statistical analyses were carried out using SPSS version 25. A normal distribution of data was used to measure the mean and standard deviation. The Mann Whitney *U* test was performed to look at the median and range of each variable if the data had a non-normal distribution. It is projected that the deviation from Hardy-Weinberg equilibrium (HWE) will be more pronounced in cases compared to controls due to the smaller number of affected people. Therefore, the studied SNP did not deviate from HWE in controls. Chi-square was used to test the deviation from HWE. Statistical significance was defined as a difference of <0.05, according to the study's results.

3. Result

This case-control study shows that patients with T1D showed a mean age (8.42 ± 2.55 years) compared to healthy controls (7.78 ± 3.03 years). Patients with T1D showed 38 (50.67%) were boys and 37 (49.33%) were girls, while healthy controls showed 31 (41.33%) were boys and 44 (58.67%) were girls. Patients with T1D showed mean BMI (16.09 ± 0.86 kg/m2) while healthy controls (15.86 ± 0.97 kg/m2). Additionally, patients with T1D showed 44 (58.67%) of urban residence and 31 (41.33%) of rural residences, while healthy controls showed 46 (61.33%) of urban residence and 29 (38.67%) of rural residence. The mean age, sex, BMI, and residency differences between T1D and control groups are not statistically significant ($P > 0.05$).In this study, 21.33% of patients had a history of diabetes in their family, while none of the controls had such a history.This was a very significant difference ($P < 0.001$) between the two groups. The mean disease duration in patients was 5.11 ± 3.41 years. The majority of patients (86.67%) were using insulin.

Conventional PCR and Sanger sequencing were performed for all the 150 samples, including cases and controls, as shown in Figs. 1 and 2.The three SNPs (rs35667974, rs35732034, and rs1990760) of the *IFIH1* region were genotyped in 75 patients with T1DM and 75 healthy control subjects. Regarding rs35667974, this position appeared in only one genotype (AA) in both patients and controls, (Fig. 3). While rs35732034 appears with the exception of one patient who had genotype AG, all other patients and controls had GG genotype, (Fig. 4). Thus, these SNPs

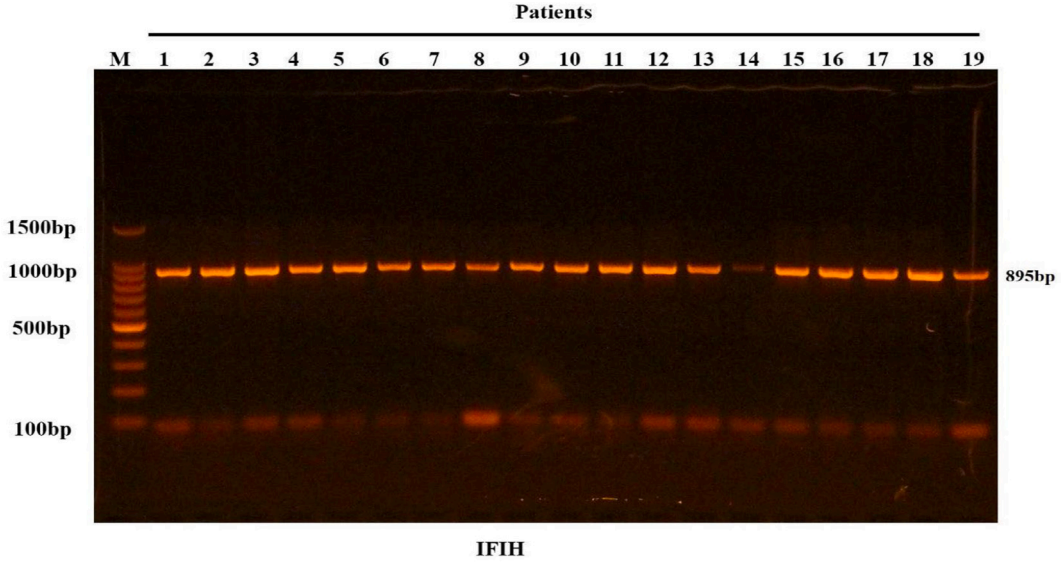

Fig. 1. Some patient samples had their IFIH gene specific region amplified on agarose (1.5%) gel electrophoresis stained with ethidium bromide. M: 100 bp ladder. 895 bp PCR products appear on Lanes 1–19.

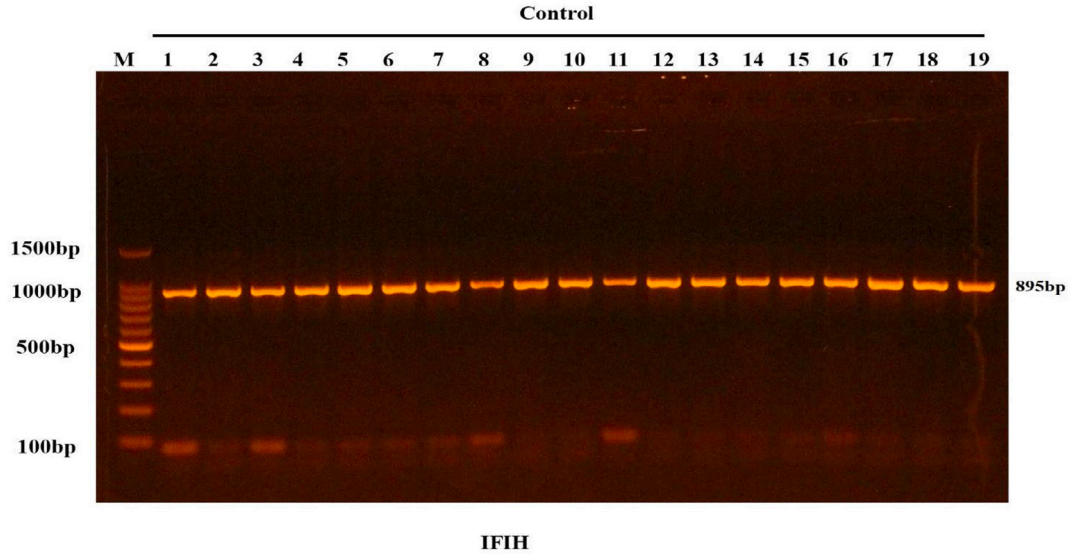

Fig. 2. Some control samples had their IFIH gene specific region amplified on agarose (1.5%) gel electrophoresis stained with ethidium bromide. M: 100 bp ladder. 895 bp PCR products appear on Lanes 1–19.

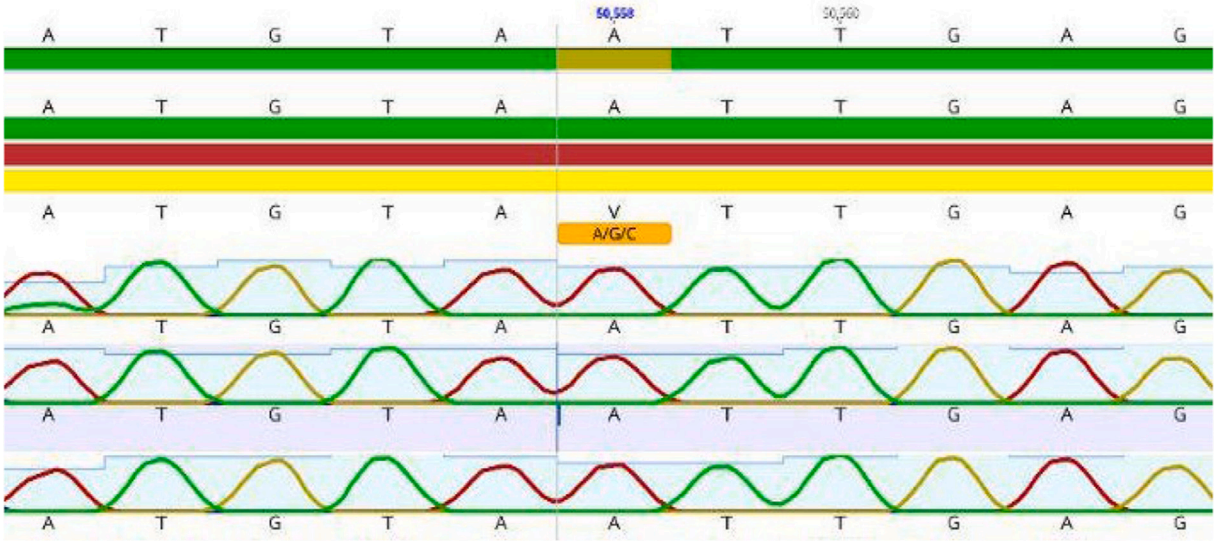

Fig. 3. Sequence analysis of the rs35667974 forward strand. The SNP had only one genotype (AA) in patients and controls.

have not undergone further analysis. However, according to the results of sequencing, the rs1990760 (A > G) SNP had three genotypes in patients and controls. These were GG, GA, and AA, Fig. 5. The distribution of different genotypes in this SNP was found to be in good accordance with Hardy-Weinberg Equilibrium (HWE).

Regarding the genotype distribution and allele frequency of rs1990760, the wild type GG genotype was more frequent in controls than in patients (32% vs. 22.67%); however, the difference was not significant. In contrast, the mutant genotype (AA) was more frequent in patients (30.66%) than controls (22.67%), with no significant difference. The present study revealed a non-significant association between the distribution of the genotype (rs1990760) in subjects of the T1D group and the control group in dominance, recessive models, or allele frequency,as shown in Table 1.

The RBS and HbA1c were significantly greater in patients (268.92 ± 86.21 mg/dl and 8.23 ± 1.76%, respectively) than in controls (113.94 ± 17.08 mg/dl and 4.76 ± 0.5%, respectively) (P < 0.001). Also, patients had greater levels of fructosamine than controls (5.42 ± 1.0 mmoml/L versus 1.91 ± 0.18 mmol/L). None of the included laboratory parameters had a significant association with distinct genotypes of rs1990760 in T1D patients or health control ($P > 0.05$) as shown in Tables 2 and 3.

The median levels of anti-Islet antigen antibody (Anti-IA2), islet cell antibody (ICA), and glutamic acid decarboxylase antibodies (GAD65) in patients were 34.8 U/ml, 32.7 U/ml, and 43.8 IU/ml, respectively, compared to 16.9 U/ml, 17.3 U/ml, and 14.8 IU/ml in controls with highly significant differences. None of the included autoantibodies tests had a significant association with distinct genotypes of IFIH1 rs1990760 in T1D patients ($P > 0.05$) as shown in Table 4 while in control group, the median ICA in GA genotype carriers was 12.8 U/ml (range = 7.9–26.1 U/ml) which was significantly higher than those of GG genotype carriers (median = 18.3 U/L, range = 9.7–27.0 U/ml) or AA genotype carriers (median = 19.0, range = 8.6–27.0 U/ml) with significant differences ($P = 0.007$), as shown in Table 5.

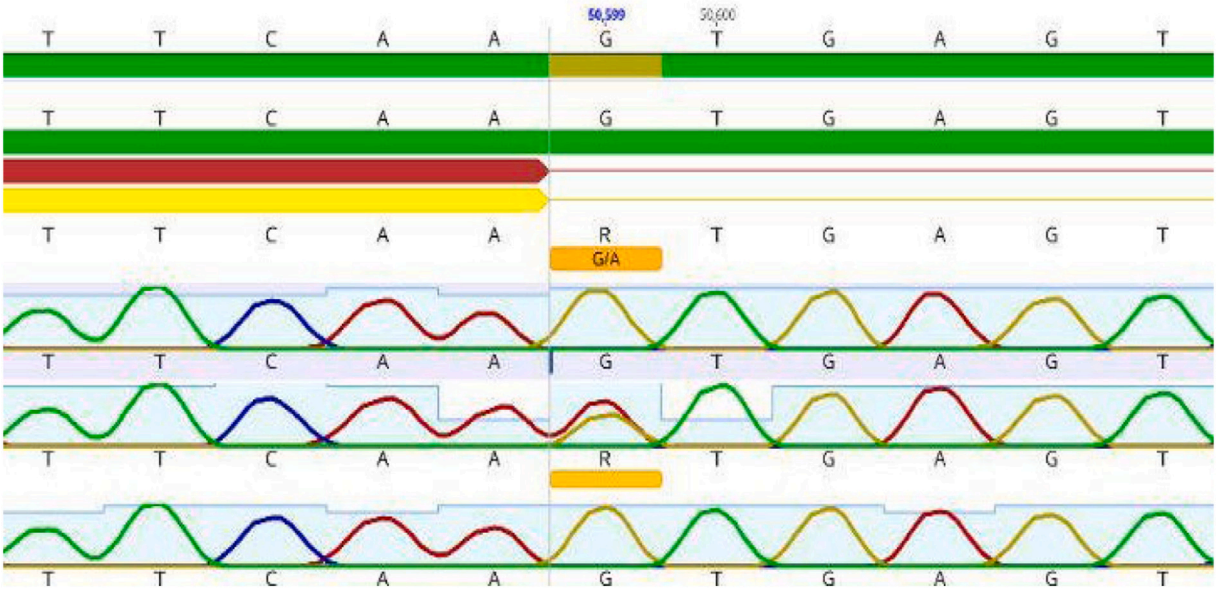

Fig. 4. Sequence analysis of the rs35732034 forward strand. The G in the upper and lower line represents homozygous wild type genotype (GG), while the R in middle line represents the heterozygous genotype (AG).

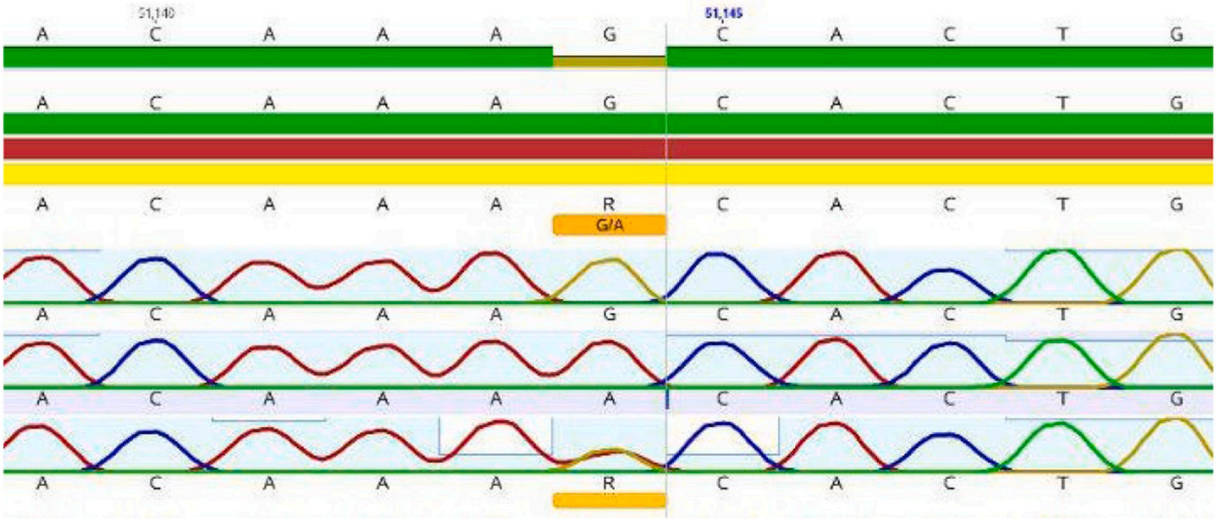

Fig. 5. Sequence analysis of the rs1990760 forward strand. The G in the upper frame represents homozygous wild type genotype (GG), the A in the middle frame represent the mutant genotype (AA), while the R in lower line represents the heterozygous genotype (AG).

Table 1
The frequency of different genotypes and alleles of the polymorphism rs1990760 among study groups.

rs1990760	Patients(75)	Controls(75)	*P*-value	OR(95%CI)
Genotypes				
GG	17(22.67%)	24(32%)	0.352	1.0
GA	35(46.67%)	34(45.33%)	0.495	1.31(0.60–2.88)
AA	23(30.66%)	17(22.67%)	0.151	1.91(0.79–4.62)
HWE	0.599	0.460		
Dominant model				
GG + GA	52(69.33%)	58(77.33%)	0.269	1.0
AA	23(30.67%)	17(22.67%)		1.51(0.73–3.13)
Recessive model				
GG	17(22.67%)	24(32%)	0.201	1.0
GA + AA	58(77.33%)	51(68%)		1.61(0.78–3.32)
Alleles				
G	69 (46.30%)	82(56.86%)	0.134	1.0
A	81(53.70%)	68(43.14%)		1.42(0.9–12.23)

Table 2
Association of numerous genotypes of the rs1990760 SNP with biochemical tests level in T1D patients.

Biochemical tests	GG(n = 23)	GA(n = 35)	AA(n = 17)	*P* value
FBS, mg/dl				
Median	250	275	225	0.419‡
Range	177–460	135–560	150–450	
Fructosamine, mmol/L				
Mean ± SD	5.27 ± 0.82	5.61 ± 1.0	5.24 ± 1.21	0.318*
HbA1c, %				
Mean ± SD	7.65 ± 1.09	8.5 ± 1.9	8.45 ± 2.08	0.173*

‡ Kruskal Wallis test.
* Analysis of variance.

Table 3
Association of numerous genotypes of the rs1990760 SNP with laboratory tests level in control.

Laboratory tests	GG (n = 23)	GA (n = 35)	AA (n = 17)	P value
FBS, mg/dl				
Median	108	113	114	0.700‡
Range	87–153	88–158	84–156	
Fructosamine, mmol/L				
Mean ± SD	1.89 ± 0.16	1.92 ± 0.16	1.91 ± 0.22	0.905*
HbA1c, %				
Mean ± SD	4.76 ± 0.54	4.71 ± 0.4	4.83 ± 0.6	0.667*

‡ Kruskal Wallis test.
* Analysis of variance.

Table 4
Association of numerous genotypes of the rs1990760 SNP with autoantibodies tests in T1DM patients.

Laboratory tests	GG(n = 23)	GA(n = 35)	AA(n = 17)	P value
Anti-IA2, U/ml				
Median	34.6	34.8	36.6	0.068‡
Range	25.9–51.9	26.8–65.3	27.9–71.2	
ICA, U/ml				
Median	34.8	32.7	32.7	0.511‡
Range	25.7–55.2	24.9–59.6	26.9–43.8	
GAD, IU/ml				
Median	45.6	43.6	47.7	0.447‡
Range	31.6–75.6	32.7–85.2	33.7–80.0	

‡ Kruskal Wallis test.

Table 5
Association of numerous genotypes of the rs1990760 SNP with autoantibodies testsin control.

Laboratory tests	GG(n = 23)	GA(n = 35)	AA(n = 17)	P value
Anti-IA2, U/ml				
Median	19.3	17.5	14.45	0.268‡
Range	7.9–26.9	7.9–25.1	6.8–27.3	
ICA, U/ml				
Median	18.3[a]	12.8[b]	19.0[a]	0.007‡
Range	9.7–25.8	7.9–26.1	8.6–27.0	
GAD, IU/ml				
Median	15.3	16.6	12.9	0.198‡
Range	7.9–25.1	7.9–24.1	8.9–14.8	

‡ Kruskal Wallis test.

4. Discussion

A higher number of siblings with T1D was found in families with a positive family history of type 1diabetes, which supports the findings of the study on familial clustering of T1D, which found that first-degree relatives have an 8–15-fold increased risk of developing TID, and second-degree relatives have an 8–20% increased risk (Albishi et al., 2021). Several other studies found a significantly elevated risk in close relatives of a patient with T1D, with an average risk of around 6% in kids, 5% in siblings, and 30% in identical twins of the patient (Alotaibi et al., 2017).

Diabetes may be influenced by genetic variations in the insulin-encoding gene (*INS*). However, these genetic variants have also been linked to alterations in insulin activity in pancreatic islets and, additionally, have consequences for beta-cell function and resilience. Other T1DM-related genetic variants may have an impact on beta-cell health, vitality, and defense mechanisms (Roep et al., 2021).

There are many genome-wide association studies (GWAS) done by the International Type 1 Diabetes Genetics Consortium (T1DGC). The data from these studies is available to the scientific community when they request it. Over 40 genes have been linked to the risk of developing Type 1 diabetes through GWAS and big meta-analyses (Diedisheim et al., 2020). In addition to antigen presentation, T lymphocytes and B cell activity, the receptor signaling complex, and scaffold activity have been found to be enriched in T1D patients. This enrichment may explain a component of their role in the etiology of T1D (Redondo et al., 2018).

Type 1 diabetes is associated with the Protein Tyrosine Phosphatase Non-Receptor Type 22(*PTPN22*) gene polymorphism (rs2476601) (Valta et al., 2020) and the SNP rs917997 of the Interleukin 18 Receptor Accessory Protein (*IL18RAP)* gene (Myhr et al., 2013), which controls interferon gamm a(IFN-γ) production. The Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4) gene polymorphism (rs3087243) (Chen et al., 2018) and the rs11755527 polymorphism in the broad complex-tramtrack-bric a brac and Cap'n'collar homology 2 (BACH2) gene (Dieter et al., 2020) that leading to T1DM development. Also the Src Kinase Associated Phosphoprotein 2 (*SKAP2)* gene (rs7804356) (Fløyel et al., 2021), a gene that may be associated with type 1 diabetes, and the Glis Family Zinc Finger 1 (*GLIS3)* gene (rs7020673) (Wen and Yang, 2017), regulates β-cell apoptosis and glycemic control in newly diagnosed patients with T1DM.

Furthermore, the interleukin-2 receptor alpha (IL2RA) gene (rs12251307 (Borysewicz-Sańczyk et al., 2020), the ERBB3 gene (rs2292239) (Lemos et al., 2018), theSH2B adapter protein 3(SH2B3) gene (rs3184504) (Auburger et al., 2014), and the Cathepsin H(CTSH) gene (rs3825932) (Ye et al., 2021) are linked to type 1DM.The interleukin 27(IL27) gene (rs4788084) (Ciecko et al., 2019) is essential for type 1 diabetes development and sjögren syndrome-like inflammation. Sharp et al., describe how Protein Tyrosine Phosphatase Non-Receptor Type 2(*PTPN2)* gene (rs1893217) and Protein Tyrosine Phosphatase Non-Receptor Type 22 (*PTPN22)* gene (rs2476601) genetic variations play a part in the etiology of type 1 diabetes and Crohn's disease, among other conditions (Sharp et al., 2015). Finally, the Ubiquitin Associated And SH3 Domain Containing A (*UBASH3A)* gene (rs11203203) influences the risk of type 1 diabetes by inhibiting TCR-induced nuclear factor kappaB (NF-κB) signaling (Ge et al., 2017).

Genome-wide interaction trials of European families with diabetes and a varied population of Caucasians from the United Kingdom were the first to show a link between the *IFIH1* gene and T1D (Pociot, 2017). The *IFIH1* SNP rs1990760 and rs3747517 have been connected to an increased risk of developing type 1 diabetes, while rs35744605, rs35744605, rs35337543, and rs35732034 have been linked to a reduced risk of developing type 1 diabetes (Mine et al., 2020).

In the *IFIH1* gene region, the most single nucleotide polymorphisms (SNPs) were found to be connected to diabetes, with marker rs1990760 particularly linked. An adenine-to-guanine substitution in exon 14 of the coding sequence resulted in a codon 946 amino acid change from alanine to threonine. Type 1 Diabetes risk was shown to be reduced in those with the minor Thr-encoding allele (Kayagaki et al., 2007).

T1D is associated with SNP markers rs1990760, rs374517, rs2111485, and rs13422767 among Caucasians from Georgia in the United States. While rs374517, found in the *IFIH1* coding region, changes the amino acid histidine to arginine at position 843 in exon 13, the other two, rs2111485 and rs13422767, are found in the intergenic space, respectively 13 kilobytes (kb) and 23 kb from the gene's end (Liu et al., 2009). Homozygous carriers of the predominant allele in all four SNPs were shown to have an increased risk of developing diabetes, with odds ratios between 1.7 and 2.3 in each instance (Kayagaki et al., 2007). There was an inverse relationship between two intergenic region markers in Canada, rs2111485A = G and rs984971A = G, both of which showed a substantial link with type 1 diabetes. The minor allele G had an odds ratio of 0.84 and 0.85, respectively (Törn et al., 2015).

Our results similar with other studies such as Jameelet al. in Iraqi population with case-control study include 100 subjects (50 T1DM and 50 healthy control) (Jameel et al., 2020), Martínezet al. in Spain popuplation which is case control study included 311 T1D and 535 control group (Martínez et al., 2008), Aminkenget al. in Belgium population with 1981 T1D, 2092 control group (Aminkeng et al., 2009) and Yang et al. in population of Han Chinese in 2012 with case control study (464

T1D and 465 control) (Yang et al., 2012) that showed no significant association between rs1990760 polymorphism withT1D, but contrast with other studies such as Bouçaset al. in Brazilian population with study 527 T1D and 517 health control (Bouças et al., 2013), Jermendy et al. in Hungarian population in 2010 which study 757 T1D, and 499 control group(Jermendy et al., 2010), Jermendy et al. in population of Central-Eastern European ancestry in 2018 with study 1055 T1D patients (Jermendy et al., 2018) and Zurawek et al. in Polish population of Caucasian origin with study number (514 TID and 713 control group) in 2015 (Zurawek et al., 2015), these studies disagree with results of present study may be due to low sample size which belong to children with newly diagnosed of T1D and inclusion criteria that chosen.

In the present study, we found that rs1990760 of the IFIH1 gene was not associated with FBS, Fructosamine, HbA1c, Anti-IA2, ICA and GAD65 in T1D patients ($P > 0.05$) as shown in Tables 2 and 4, also, the results of the control were similar to the results of T1D patients except that the ICA result was associated with rs1990760 of the IFIH1 gene ($P = 0.007$) as shown in Tables 3 and 5. The present results were agree with several studies such as Jameel *et al.* in Iraqi patients (Jameel et al., 2020), Aminkeng*et al.* in Belgian residents (Aminkeng et al., 2009), Boucas *et al.* in Brazilian population (Bouças et al., 2013) and Majeed*et al.* in Iraqi population (Majeed et al., 2021), but contrasts with that found with other studies the significant associated with the above laboratory tests in T1D patients such as Kochenborger *et al.* in Brazil (Kochenborger et al., 2015), Wawrusiewicz-Kurylonek*et al.* in Poland (Wawrusiewicz-Kurylonek et al., 2020), Lempainen*et al.* in Finland (Lempainen et al., 2015) and Plagnol*et al.* in United Kingdom (Plagnol et al., 2011).

There is some agreement between the findings of our present investigation and those of the previously published cohorts. However, the rs1990760 SNPs' relevance tends to vary across cohorts, and there are some variations in the impacted phase between publications. Some of these variations can be explained bythe relatively huge number of SNPs tested in a small sample series,caused byprobability associations as well as lack of detection due to the low significance of the studies (Lempainen et al., 2015). The prevalence of type 1 diabetes varies by nation. The studied SNPs, which comprised HLA class II and non-HLA risk genes, could not explain most of the observed discrepancies. When it comes to determining whether genetic effects are apparent in each geographical location, environmental variables and gene-environment interactions may be helpful (Lempainen et al., 2015).

The present study is novel because there is scant literature in that field of *IFIH1* in Iraq. We would, therefore, provide additional insight into that field of knowledge. It is also novel because it has been done recently in my country. This is the first study in Iraq that uses molecular methods (PCR and sequencing) to look at the relationship between type 1 diabetes and the *IFIH1* gene in newly diagnosed children. The previous studies in Iraq that looked at the same thing used serological methods (measuring the protein of the *IFIH1* gene for all participants, regardless of their age or how long they had been diagnosed).

5. Conclusion

The current results indicate that the *IFIH1* rs35667974, rs35732034 and rs1990760 polymorphismsare not associated with T1D in Iraqi children, and the IFIH1 SNP rs1990760 was found to have three genotypes. These were GG, GA and AA. It is necessary to conduct more research on a large number of Iraqi people in order to accurately analyze the connection between *IFIH1* genotypes and illness development and to investigate the role and effect of otherdifferent SNPs of *IFIH1* that lead to predispose and developing T1DM.

6. Limitations

The sample size in the current study is small, i.e., 75 children were recently diagnosed with Type 1 diabetes mellitus (T1DM) and 75 healthy controls, and this must be considered a limitation to the current study. This due to the spread of the Corona pandemic during the period of sample collection, when there was a presence for people to roam and people to stay in their homes, except for humanitarian and health cases. Also the quality of the samples that are supposed to be collected for the study; they are newly diagnosed children with type 1 diabetes, and this reduces the number of samples and the difficulty of obtaining them. In addition, some parents of children with type 1 diabetes refuse to draw blood from their children for fear of what it might do to them, and this limits the number of samples required. Hence, a larger sample size is needed to further refine the research results.

Author contributions

All authors contributed to the study's planning, design, analysis, and interpretation.

Funding

Self-funding.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

Thanks to the laboratory staff in the diabetic and endocrine glands center and Bint Al-Huda Children's Hospital in ThiQar governorate for their cooperation in accomplishing this study.

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Further reading

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