

Original Research

Determining the Role of KRAS in Patients with Different Demographic Profiles Diagnosed with Diabetes Mellitus: A Case-Control Study

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Abstract

Diabetes mellitus (DM) is widely spread among populations. About 3 of 10 people show the symptoms of this disease. Many factors may cause this illness in both types (type 1 and type 2 DM), mainly attributed to insufficient insulin production in type 1 DM or developing insulin resistance in type 2 DM. Genes that control specific biochemical pathways involving glucose metabolism can interfere with the manifestation of this disease when they undergo genetic changes like KRAS. Investigating the role of KRAS in DM. About 124 patients with both types of DM and of different genders and ages participated in this study. In addition to



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demographic characteristics, biochemical and diabetic status were determined for all participants. DNA was isolated from all patients, and the KRAS gene was amplified using specific primers designed for this purpose and thoroughly analyzed to determine any genetic change within its sequence. The results showed the spread of DM, especially type 2, among undereducated participants, and a significant increase in fasting blood sugar, uric acid, and SGOUT. Molecular analysis of the KRAS gene identified two repeated single-nucleotide variations (SNVs): rs1475732807 and rs1306089842. Both SNVs affected the 3' UTR of the KRAS gene, causing an alteration in gene expression, which consequently affected the severity of DM. Diabetes mellitus is widely spread among different societies, especially in undereducated groups, due to unhealthy diets or genetic factors. Some genes, like KRAS, can interfere with the manifestation of DM, especially related to glucose metabolism. SNVs in the 3' UTR of KRAS may dramatically boost the symptoms in some patients.

Keywords

Diabetes mellitus; insulin deficiency; insulin resistance; KRAS; epigenetic

1. Background

Chronic hyperglycemia is a metabolic disorder represented by a lack of, or increased secretion of, insulin or impaired hormone function. Insulin is considered an anabolic hormone that affects the metabolism of carbohydrates, lipids, and proteins [1]. The abnormality in insulin function affects tissues such as the liver, skeletal muscles, and adipose tissue due to insulin resistance [2]. Statistics published by the WHO in 2014 showed that 8.5% of adults aged 18 and above were diagnosed with diabetes, with increased mortality in 2019 caused by this disorder reaching 1.5 million deaths [3]. Diabetes mellitus (DM) can be classified into several types. Type 1 (T1DM) can be detected well before abnormal insulin secretion begins. When this type begins, a significant glucose variation can be seen. It involves immune-mediated destruction of β -cells, leading to a deficiency in insulin levels. Successful T1DM management requires an interprofessional approach to patient care, self-management education, and replacement therapy [4]. Another type of DM is the idiopathic T1DM, which is considered a rare variant of T1DM that is found in African and Asian groups, in which patients may show ketoacidosis in addition to insulin deficiency [5]. Type 2 diabetes mellitus (T2D) is a condition where the body becomes resistant to the physiologic effects of insulin and gradually loses the ability to produce enough insulin to compensate for the body's needs. In this case, the sugar builds up in the blood. T2DM patients have a high proinsulin-to-insulin (C-peptide) ratio [6]. Hyperglycemia worsens over time and becomes more difficult to treat [7].

Among other causes of DM, tumors in the pancreatic region may lead to this metabolic disorder [8]. Such tumors are mainly attributed to mutations in the RAS genes (KRAS, HRAS, and NRAS) [9]. The GTPase KRAs (KRAS) function as a signal transducer protein that interferes in various cellular signaling pathways, such as cell proliferation, and acts as a critical hub in some biological processes, such as the mitogen-activated protein kinase (MAPK) pathway [10]. Mutations and other proteins that hyperactivate RAS may lead to the cancer manifestations of

RASopathies [11]. KRAS accounts for about 85% of mutated RAS proteins observed in malignancies [12]. In a previous report [13], inhibiting oncogenes or their downstream mediators can be lethal to metabolically addicted cells without causing any harm to normal cells. The mutated KRAS can increase the transport of glucose via the glucose transporter 1 (GLUT1). This may trigger the glycolytic activity by limiting glycolytic enzymes such as hexokinase, phosphofructokinase 1, and lactate dehydrogenase [14]. This will shut down the glycolytic intermediates into the hexosamine biosynthesis pathway [15].

In most cases, the evaluation of KRAS in patients with T2DM took place in patients diagnosed with colorectal, pancreatic, and breast cancer [16]. Thus, the idea behind this work is to evaluate the KRAS gene in cancer-free T2DM patients.

1.1 Research AIM

Given KRAS's biological function, we intend to investigate its role in diabetes in non-cancerous cases.

2. Materials and Methods

2.1 Place and Period of the Research

Place of the research. This research was conducted at the Biotechnology Research Center, Al-Nahrain University, Department of Environmental Biotechnology, and the Molecular Biology Lab.

Period of the research. The research was approved by the Biotechnology Research Center IRB on 2.1.2022 for a two-year period.

2.2 Populations under Study (One or More)

Population. The study included 124 patients with diabetes and 50 healthy persons. The participants were of different ages, genders, and backgrounds.

Inclusion criteria: Participants were diagnosed with DM of either type, regardless of gender or age.

Exclusion criteria. Participants taking beta-blockers, Glucocorticoids, Thiazide diuretics, or any kind of drugs that may cause diabetes were excluded from this study. In addition, Patients with pancreatic tumors, colorectal cancer, or any disease affecting normal glucose rate in the body, and women who developed diabetes during pregnancy were also excluded from the test group.

2.3 Method of Sampling from the Studied Population

About 5 ml of blood was withdrawn from each participant. These blood samples were the source for clinical tests and DNA used during this study.

2.4 Study Design

The study was designed on two bases:

First, studying and recording the clinical factors presented by patients, the demographic distribution of participants, and the degree of education.

Second, the KRAS gene sequence in patients was compared with that of healthy individuals.

2.5 Methods

2.5.1 Source of DNA

The DNA from participants was obtained by withdrawing 5 mL of blood through a puncture wound. A 200 µl of the sample was used for DNA extraction using the Genaid blood DNA extraction kit following the company's instructions. A sufficient quantity of the sample was used for biochemical analysis. The remaining blood samples were kept in sterile EDTA tubes at -20°C.

2.5.2 KRAS Targeting Primers

Primers used to target the KRAS gene were designed depending on the gene sequence available at the NCBI website under accession no. M54968.1:193-759.

2.5.3 Conventional PCR Primers

We used 4 sets of primers to target the KRAS gene with the following sequences

K1F: 5'GTCTCCCTGTGTCAGACTGC3'; K1R: 5'AATGTCTTGGCACACCACCA3';

K2F: 5'TCCCTGTGTCAGACTGCTCT3'; K2R: 5'AGGACCACCACAGAGTGAGA3';

K3F: 5'AGGGACTAGGGCAGTTTGGA3'; K3R: 5'CACCTACCATGCCATCTCA3';

K4F: 5'TCTCCCTGTGTCAGACTGCT3'; K4R: 5'ACCTACCATGCCATCTCAC3'.

2.5.4 Real-Time PCR Primers

The following primers were designed for Real-Time PCR amplification. Amplicon size 165 bp, and SYBR Green was used during the amplification process as an amplification reporter.

KRASRTF TGTGGTAGTTGGAGCTTGTG, TGACCTGCTGTGTCGAGAAT

2.5.5 Conventional PCR Amplification Program

The target gene was amplified by LabNet Thermocycler (USA) using the following PCR conditions: 1 cycle of initial denaturation at 94°C followed by 35 cycles of denaturation at 95°C for 30 sec, annealing at 57°C for 30 sec, and extension at 72°C for 30 sec. After the cycles were complete, the mixture was left to extend at 72°C for 10 min, then cooled to 4°C and removed. The samples were kept at -20°C until resolved by electrophoresis at 8 v/cm field strength for 45 min using 1.5% agarose.

2.5.6 Real-Time PCR Amplification Program

The target gene was amplified by Applied Biosystems RT-PCR (USA) via one-step reverse transcriptase-qRT-PCR (Invitrogen SuperScript IV UniPrime) following company instructions to generate the first strand, while the following program was employed for qRT amplification: denaturation at 95°C for 5 sec, annealing at 55°C for 30 sec, and extension at 72°C for 30 sec. After the amplification step ended, the melting curves were generated.

2.5.7 Housekeeping Gene

The beta-actin gene was used as a reference to quantify differences in gene expression. The following primers were designed during this work:

act-F CACCATGTACCCTGGCATTG

act-R CCTGCTTGCTGATCCACATC

2.5.8 Data Analysis and Bioinformatics Tool

Data analysis was performed using BLASTRef Sequence, BLASTX, and BLASTP, available tools at <https://www.ncbi.nlm.nih.gov> to track changes in DNA sequence, BLAT, and TBLASTN at <http://asia.ensembl.org> to locate the chromosomal change site, and a tracking tool from BLAST results was used at http://genome.cse.ucsc.edu/cgi-bin/hgBlat?hgsid=1156794913_Jd6ALd0brGcqEABzVfUKN0dtPdVA&command=start to illustrate the pathogenic effect of the DNA change.

2.6 Statistical Analysis

Statistical analysis was performed using MiniTab software version 19.

2.7 Ethics Review

The Biotechnology Research Center IRB approved this research under No. E. B. 6 in 1.2022.

All participants in this work were asked to sign a written participation consent form. The Helsinki Declaration was followed during sample collection and the preservation of personal data.

3. Results

In this work, 124 participants with DM were included in the demographic and genetic analyses of the KRAS gene. The demographic analysis is given in Table 1. Most participants were female, reaching 66.1% of all participants. The mean age was 52 years, with subjects younger than 65 years of 87%.

Table 1 Demographic Characteristics.

Gender	n (%)
Females 82	(66.1)
Males 42	(33.9)
Age (yrs)	
Mean	52
Range	20-80
Education	
Grade school or less	65 (45.8)
Completed high school	45 (29.7)
Beyond high school	14 (11.0)

3.1 Diabetic Status

A ratio of 91% (107 participants) of 118 were of T2DM, as shown in Table 2. Patients with T1DM were significantly younger than those with type II (mean age 34.5 years, vs. 53.7 years, $P < 0.001$). The table shows that 11 patients with T1DM had a 10-year diabetic duration when compared with 28 (26.2%) of 107 patients with T2DM ($P > 0.004$). Among the 107 patients, 38% were taking insulin at the time of sample collection.

Table 2 Clinical Characteristics.

Characteristic	Type I (n = 11) [no. (%)]	Type II (n = 107) [no. (%)]	Total (n = 118) [no. (%)]
Age (yrs)			
20-40	8 (72.7)	12 (11.2)	20 (16.9)
41-50	3 (27.5)	31 (29.0)	34 (28.8)
51-60	0	35 (32.7)	35 (29.7)
60+	0	29 (27.1)	29 (24.6)
Duration of diabetes mellitus			
New onset	0	24 (27.4)	24 (20.3)
Less than 2 yrs	0	45 (42.1)	45 (25.1)
2 yrs or greater but less than 5	0	16 (15.0)	16 (13.6)
5 yrs or greater but less than 10	3 (27.3)	18 (16.8)	21 (17.8)
10 yrs or more	8 (72.7)	28 (26.21)	36 (30.5)
Diabetes Treatment			
Diet	0	9 (8.4)	9 (7.6)
Oral hypoglycemic	2 (15.2)	62 (57.9)	64 (54.2)
Insulin	9 (80.8)	36 (33.6)	45 (38.1)
Prior hospitalization			
Yes	9 (81.8)	69 (64.5)	78 (66.1)
No	2 (18.2)	38 (25.5)	40 (33.9)
Family history			
Yes	10 (90.9)	58 (54.2)	68 (57.6)
No	1 (9.1)	45 (42.1)	46 (39.0)

3.2 The Biochemical Characteristics of Diabetic Patients

The biochemical parameters of patients with diabetes who participated in this study are shown in Table 3. The table shows a significant elevation in fasting blood sugar compared to the normal value, whereas total cholesterol and LDL-Cholesterol showed insignificant elevation compared to the normal. We noticed that VLDL-Cholesterol and SGPT were significantly elevated ($P > 0.04$).

Table 3 Biochemical characteristics of patients with DM under study.

Parameter	Mean $\pm$ SD	95% CI	Clinical reference value	Δ vs reference	Effect size (d)	p-value*	Clinical interpretation
Fasting plasma glucose (mg/dL)	251.51 $\pm$ 112.08	201.6-301.4	70-100	$\uparrow$ markedly elevated	1.62	<0.001 [†]	Severe hyperglycemia
Glycated hemoglobin (HbA1c, %)	8.25 $\pm$ 0.25	8.13-8.37	<5.7	$\uparrow$ elevated	2.10	<0.001 [†]	Poor long-term glycemic control
Total cholesterol (mg/dL)	219.59 $\pm$ 68.25	189.3-249.8	<200	$\uparrow$ elevated	0.89	0.001 [†]	Hypercholesterolemia
Triglycerides (mg/dL)	196.44 $\pm$ 94.34	154.6-238.3	<150	$\uparrow$ elevated	0.76	<0.001 [†]	Hypertriglyceridemia
HDL-cholesterol (mg/dL)	35.14 $\pm$ 11.85	29.9-40.4	$\geq$ 60	$\downarrow$ reduced	-1.18	<0.001 [†]	Low protective HDL
LDL-cholesterol (mg/dL)	145.72 $\pm$ 64.33	117.2-174.3	<100	$\uparrow$ elevated	0.71	0.001 [†]	Increased cardiovascular risk
VLDL-cholesterol (mg/dL)	40.88 $\pm$ 18.12	32.9-48.9	5-30	$\uparrow$ elevated	0.84	0.004 [†]	Elevated triglyceride-rich lipoproteins
Uric acid (mg/dL)	3.45 $\pm$ 1.51	2.78-4.12	3.4-7.0	$\approx$ within range	0.03	0.001 [†]	No major deviation
Creatinine (mg/dL)	0.86 $\pm$ 0.37	0.70-1.02	0.6-1.3	$\approx$ within range	0.04	<0.001 [†]	Normal renal function
Urea (mg/dL)	29.16 $\pm$ 9.81	24.8-33.5	15-45	$\approx$ within range	0.08	0.001 [†]	Within physiological range
Total bilirubin (mg/dL)	0.87 $\pm$ 0.40	0.69-1.05	0.1-1.2	$\approx$ within range	0.06	0.001 [†]	Normal liver metabolism
Direct bilirubin (mg/dL)	0.48 $\pm$ 0.40	0.30-0.66	0-0.5	$\uparrow$ borderline	0.12	0.001 [†]	Mild elevation
AST (SGOT) (IU/L)	37.15 $\pm$ 10.90	32.3-42.0	8-45	$\approx$ within range	0.10	0.089 [‡]	Not statistically significant
ALT (SGPT) (IU/L)	35.83 $\pm$ 23.04	25.6-46.1	7-56	$\approx$ within range	0.18	0.006 [†]	Mild elevation

* p-values were calculated using a one-sample Student's t-test, comparing the mean biochemical values of the patient cohort with established clinical reference values. [†] Statistically significant (p < 0.05). [‡] Not statistically significant. Values are presented as mean $\pm$ standard deviation (SD) with 95% confidence intervals (CI). Effect size (Cohen's d) represents the standardized difference between observed mean values and reference values.

Patients with diabetes mellitus exhibited marked metabolic dysregulation. Fasting plasma glucose and HbA1c levels were significantly elevated compared with clinical reference values ($p < 0.001$), indicating poor glycemic control. Dyslipidemia was also evident, characterized by significantly increased total cholesterol, triglycerides, LDL-cholesterol, and VLDL-cholesterol levels, accompanied by a marked reduction in HDL-cholesterol ($p < 0.001$). Renal function indicators showed statistically significant differences, including uric acid, creatinine, and urea levels. Liver function markers demonstrated significant variation in total bilirubin, direct bilirubin, and ALT activity, while AST levels did not differ significantly from the reference range ($p = 0.089$). Collectively, these findings highlight the presence of severe hyperglycemia and diabetic dyslipidemia in the study population.

3.3 Molecular Analysis of the KRAS Gene in Patients with DM

3.3.1 Real-Time Analysis

Patients' and control DNA were subjected to Real-Time PCR analysis to measure KRAS expression in both groups. The data obtained showed lower gene expression than in the control group. The melting point curve confirmed the presence of DNA changes in patients, as evidenced by different melting temperatures, as shown in Figure 1.

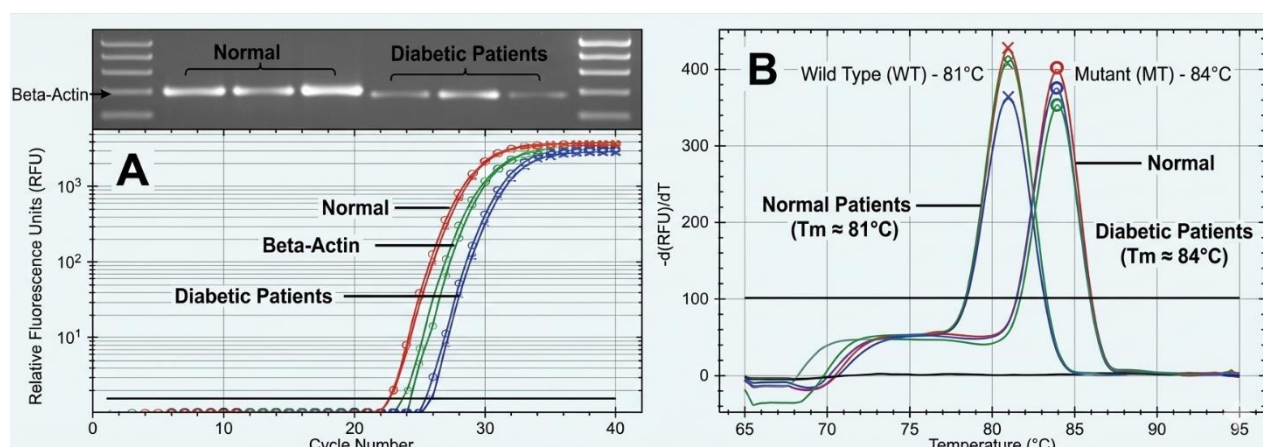


Figure 1 qRT PCR of KRAS gene shown in part (A), and melting curve of the gene as given in part (B).

3.4 Conventional PCR Amplicon Sequence Analysis and Detection of SNPs

The DNA from 124 patients with DM was used to amplify the KRAS gene using specific primers designed for this purpose. The PCR amplicons were sequenced and thoroughly analyzed to identify the types of single-nucleotide variations (SNVs) present. Our findings revealed a consistent pattern of SNVs across all patients, as shown in Table 4.

Table 4 Genetic variants detected in the investigated locus among patients with diabetes mellitus.

Variant class	dbSNP ID	Genomic position (hg38)	Reference allele	Alternate allele	Functional annotation	Genotype counts (n)	Minor allele frequency (MAF)	HWE p-value
SNP	rs1475732807	chr12:25208555	T	C	3' UTR variant	TT = 32, TC = 12, CC = 0	0.135	0.74
Indel	rs1306089842	chr12:25208517-25208520	TAAT	T	3' UTR variant	NA	NA	NA

4. Discussion

Hospitals are the primary treatment and medical care source for people with DM. The sociodemographic cohort results in this study are significant for gender, educational status, and age. About 95% of our study cohort has low-grade educational status, suggesting a population at high risk of developing DM due to an unhealthy diet [17]. Combining this factor with genetic defects in β -cells [18] and insulin receptors [19] will make these diseases unavoidable consequences.

Worldwide, the prevalence of diabetes has increased and, therefore, has grown in severity as a public health problem. Multiple risk factors are involved in the actual onset of the disease. Genetics, atmosphere, loss of the very first phase of insulin release, sedentary lifestyle, lack of physical exercise, smoking, alcohol use, dyslipidemia, reduced β -cell sensitivity, hyperinsulinemia, and increased glucagon activity are the primary risk factors for prediabetes and DM, as they contribute to insulin resistance [20].

The association of hyperuricemia and the development of T2DM has been investigated in several studies. In subjects with hyperuricemia and insulin resistance, β -cell function is triggered from its compensatory state. In another study, comparing four groups (control, T2DM: with and without obesity, and T1DM), C-peptide levels were found to increase in patients with T2DM and obesity. It appears that uric acid behavior is closely related to β cell function [21].

On the other hand, in recording patients' data, biochemical characteristics showed a significant elevation ($P < 0.001$) in fasting sugars in both genders, a traditional feature of the disease, and VLDL-triglyceride ($P < 0.004$), with a slight increase in triglycerides. It is worth mentioning that patients with a severe form of DM are highly likely to develop gout. The biochemical data show a non-significant increase in SGOT ($P < 0.089$) and SGPT ($P < 0.006$) in patients with this type of DM.

In investigating the genetic origin of DM, researchers focused on the CAPN10 gene, which encodes calpain-10, a calcium-dependent cysteine protease associated with type 2 diabetes (T2DM) risk and insulin resistance. Results showed the presence of three genotypes that were significantly associated with insulin resistance [22].

There are a few reports about the association between diabetes and KRAS mutation so far, and the results are inconclusive [23]. A recent study showed a tendency of positive association between abnormal HbA1C [≥ 48 mmol/mol (6.5%), the cut-off for diagnosis of T2DM] and KRAS mutation [24].

Surveying the DNA of the participating cohort for genetic changes in the KRAS gene identified two SNVs: rs1475732807 and rs1306089842, and a deletion. Both SNVs are located on chr 12, 32 nucleotides apart, and were detected in all participants. The rs1475732807 is predicted with severe consequences of 3' UTR variant Alleles T/C|Ancestral: T|Highest population MAF: <0.01 , and the same consequence was recorded to rs1306089842 with different characteristics to be alleles TAAT/T|Ancestral: TAAT|Highest population MAF: <0.01 . The change in the 3' UTR variant hurts mRNA transcribed from the gene, and since KRAS is known to affect glucose metabolism [25], such an effect may reflect its consequences on the DM level of severity.

Mutant KRAS increases the expression of glucose transporter 1 (GLUT1) and rate-limiting glycolytic enzymes, including hexokinases, phosphofructokinase 1 (PFK1), and lactate dehydrogenase A (LDHA), promoting glycolytic activity and increasing lactate production [26]. By upregulating these enzymes, mutant KRAS triggers the shunting of glycolytic intermediates into

the hexosamine biosynthesis pathway (HBP) to generate UDP-N-acetylglucosamine (UDP-GlcNAc) for glycoprotein, glycolipid, proteoglycan, and glycosylphosphatidylinositol [27].

In this case, gene expression, especially at the downstream site, may be downregulated, leading to reduced glucose metabolism. In previous reports [28-32], five functional SNPs located on 3' UTR may affect RAS family genes to cause haemostatic cascade changes due to modification to this site [33].

Although the present study provided valuable information regarding the association between T2DM and *KRAS* gene mutation, it has some limitations, including the absence of some variables such as the duration of T2DM and history of other comorbid conditions. The size of the population studied may not be sufficient to generalize the data. Another limitation is that most patients who attended the hospital and participated in this study stopped attending for periodic checkups after receiving their medication prescription, which makes it difficult to follow up on the progression of their cases and health status.

5. Conclusion

Diabetes mellitus is a widespread disease among populations. It is either type 1 or type 2, which is more widespread than type 1. In many cases of type 2 DM, patients may develop gout due to the elevation of uric acid. The *KRAS* may play a vital role in the severity of DM due to its involvement in glucose metabolism. Two types of SNPs were found in all patients with DM. Both SNPs affect gene expression by influencing the 3' UTR region, causing downregulation of the *KRAS* gene, leading to more severe symptoms.

Author Contributions

N.A.H conceptualization, R.S.R supervision, K.S.A. software, R.N.A writing the original draft, S.S.T data curation, R.A.K sample collection. All the authors approved the final version of the article before the publication and expressed their consent to be responsible for all aspects of the work, which implies proper investigation and resolving of issues related to the accuracy or integrity of any part of the work.

Competing Interests

This work was completed with no conflict of interest among authors.

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