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CDKAL1 SNPs (rs10946398 and rs9356744) Variations in type 2 diabetes and its association with some glycemic parameters

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ABSTRACT

Background: CDKAL1 is one of the most often discovered genes linked to risk Across a wide range of ethnic groups, investigations of genome-wide associations indicate that the gene CDKAL1 has a number of SNPs that raise the risk of type 2 diabetes (T2D).

Objective: Study the association between type 2 diabetic (T2DM) and CDKAL1,Study the effect life style on the patient of type 2 diabetic (T2DM) and Describe the association betweenCDKAL1 and T2DM pathophysiology

Methodology : a case control study these study contours 50sample control and 60 patients, Physiological parameters were measured and flanking sequencing

Result: the results showed according to diet control all parameters (age, Body Mass Index (BMI), duration, Fasting Blood Glucose (FBG), $Hemoglobin_{A1c}$(HBA1C), , Insulin hormone(IN), insulin resistance(IR), and insulin sensitivity (IS) are nonsignificant in control and patients ($p<0.05$) . in study subjects according to family history all parameters. Age , BMI, duration, FBG , HBA1C , IN and IR, are not significant while IS is significant. in study subjects according to physical activity all parameters age, BMI, duration, FBG, HBA1C, IN, IR, and IS are nonsignificant in control and patients, . the CDKAL1 genotyping showed cdkrs10946398 and cdkrs9356744 is nonsignificant.

Conclusion: no significant association between (cdkrs10946398 and cdkrs9356744)in CDKAL1 Gene and Physiological parameters age, duration , BMI , FBG , HBA1C , IN , IR and IS.

Keywords: rs10946398, rs9356744 , CDKAL1, Diabetes Mellitus Type 2(T2DM)

INTRODUCTION

Diabetes Mellitus Type 2 and Variants of CDKAL1 Do You Correlated One significant protein, known as CDKAL1 or Similar to 1, CDK5 regulatory subunit related protein 1 has been connected to the pathogenic development of sort 2 diabetes. Protein 1 is related with the regulatory component of cyclin-dependent kinase 5. (CDK5RAP1)-like 1 is encoded by the CDKAL1 gene. Because it aids in maintaining regulation of the release of insulin in a glucose-dependent mechanism, a serine or threonine protein kinases known as cyclin-associated kinase 5 (CDK5) is implicated in the β-cell pathophysiologyfailure and the susceptibility to diabetes type 2 (T2DM) (1).

CDKAL1 is one of the most often discovered genes linked to risk Across a wide range of ethnic groups (2). the several tRNA changes, investigations of genome-wide associations indicate that the gene CDKAL1 has a number of SNPs, or single nucleotide polymorphisms that raise the risk of type 2 diabetes (T2D). These SNPs affect reduced insulin production but not peripheral insulin sensitivity(3).There exist a few exceptions to the broad rule that alterations in distinct cytoplasmic tRNA modification enzymes may have an effect on the brain. For example, the majority of studies link CDKAL1 SNPs to diabetes type 2; however, Protein 1-like 1 (CDKAL1), related with the CDK5 regulatory subunit halt functioning is only associated with the production of hormones from pituitary adenomas and is not associated with any other known brain effects (4).

It is yet unclear how CDKAL1 primarily affects pancreatic β-cells' ability to produce insulin as opposed to other organs. Nevertheless, β-cell dysfunction in the setting of CDKAL1 failure could be connected to the heightened need for proinsulin translation in β-cells. When the bacterial CDKAL1 homolog was knocked out, an enhanced translation rate resulted in a decrease in lysine in a bacterial lysine translation reporter technique. Given that lysine is located in an essential location in the proinsulin protein and that proinsulin translation accounts for

approximately half of all protein production in response to glucose stimulation, it makes economic sense that β-cells would be more vulnerable to the CDKAL1 deficiency than other organs , Gene variants are linked to decreased production of insulin, but not to obesity or insulin resistance. Prior studies have not revealed the physiological activities of Cdkal1, but recent findings indicate that it is a human methylthiotransferase located at position 37 of tRNA(Lys)(UUU) that biosynthesizes 2-methylthio-N(6)-threonylcarbamoyladenosine (ms(2)t(6)A). A mutation in You need tRNA(Lys)(UUU). when translation rates are high in order to prevent misreading of the relevant codons. Animals lacking cdkal1, both in general and specifically in the pancreatic β-cell, have reduced ATP production in mitochondria and first-phase insulin production. Additionally, in the β-cell-specific knockout animals, there is evidence of decreased blood glucose and pancreatic islet hypertrophy regulation.

The accumulation of misfolded insulin, that causes oxidative stress. and endogenous receptor stress in the pancreatic β-cells and ultimately their death, has been attributed to mutations in the Cdkal1 transcript. According to a recent research, Cdkal1 may possess intrinsic thiomethyl transferase activity, which is required for pre-proinsulin to be economically broken down post-translationally to produce mature insulin. Moreover, it has been demonstrated that Cdkal1 functions as an endogenous inhibitor of Cdk5, transferring PDX1 from the nucleus to the cytoplasm and preventing the stoppage of insulin production caused by Cdk5. Current clinical investigations have demonstrated that the risk single nucleotide polymorphisms (SNPs) of Cdkal1 are a major factor contributing to the development of diabetes-related issues (5).

Many SNPs linked with type 2 diabetes have been discovered in the CDKAL1 gene through whole genome association studies (6,7).

Recent research (8) shows that in Asian and Caucasian populations, but not in African ones, there is a substantial correlation between ethnic heritage and T2D susceptibility and CDKAL1 mutations. This suggests that it is critical to validate the connection between these mutations moreover, the danger of Diabetes type 2 in a range of ethnic populations. Furthermore, research is needed to ascertain if non-genetic factors play a role in the association between Diabetes type 2 and CDKAL1 SNPs. Here, we looked at the connections between T2D risk factors include age, gender, body mass index (BMI), alcohol use, and smoking., and CDKAL1 polymorphisms using a case-control research. We further examine the association between the clinical features of T2D patients and CDKAL1 SNPs among the Northwest Chinese Han people. For example, no research has been published evaluating the effect of the effects of the T2D susceptibility SNPs rs10440833 and rs35612982 on CDKAL1 in a Chinese Han population.

MATERIALS AND METHODS

Study design: There are 50 control subjects and 60 cases in the case control study. These samples used for DNA extraction from blood cells.

Ethical approval: all contributors enrolled in the present study with written consents according to ethical approval code B240302 of ministry of higher education and scientific research.

DNA isolation: relying on the FAVORGEN kit following DNA extraction, which is followed by gal electrophoreses and polymerase chain reaction (PCR)

primer sets were used to amplify the sequencing analyses of the following SNPs:**cdkrs10946398** F1-CAG GAT CTT GTG CTC CTC AC R1-CCA ACA GCA AGC AGT TGA TT F2-GGA AAA GGG TTT AGT ATC GCT C R2-GAT GAC TTG ATG CAA TGA CAG TAT , cdkrs9356744 f-TTGTCAAACCTAAGGGCATCT r- AAGGCTTTCTGCAAAGCAAC

the identification of the ideal annealing temperature need to amplify cdkrs10946398, Initial denaturation in 95℃ for 5min , Denaturation in 95℃ for 0:30min, annealing primer in55 ℃ for 0:40 min , the Extension of the template in 72℃ for 0:40 min , Last extension in 72℃ for 5 min all of these occurs in 30 cycles and incubation in 4℃.in the SNP cdkrs9356744 the identification of the ideal annealing temperature need to amplify for , Initial denaturation in 95℃ for 5min , Denaturation in 95℃ for 0:30min, annealing primer in57 ℃ for 0:40 min , the Extension of the template in 72℃ for 0:40 min , Last extension in 72℃ for 5 min all of these occurs in 30 cycles and incubation in 4℃.

RESULTS

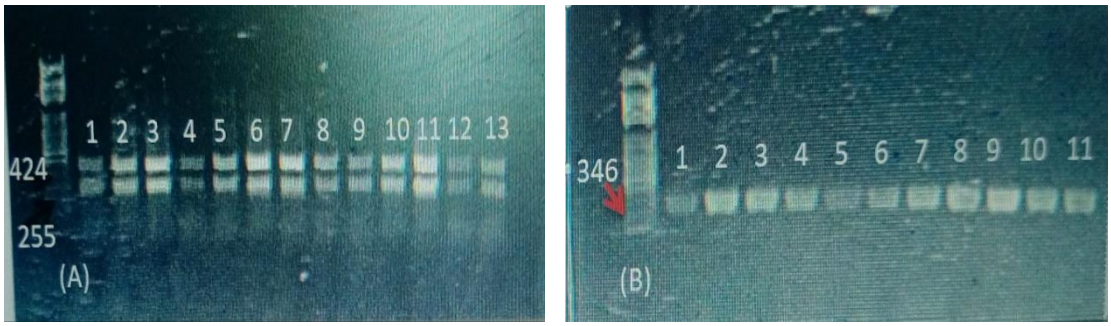

Figure 1:(A) mean The results of The SNP cdk10946398 showed that the Polymerase chain reaction product had two band about (424 and 255).(B) mean The results of The SNP cdkrs9356744 showed that the Polymerase chain reaction product had one band about (346).

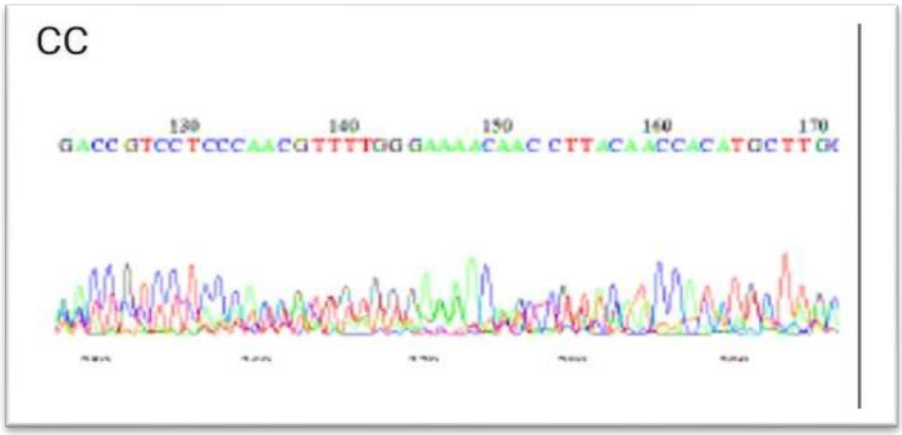

Figure 2: mean The results of The SNP cdkrs9356744 showed that the sequencing gene product Has heterogeneity in location(CC)

differences in biomarkers in study subjects according to diet control

Results of statistical analysis elucidate all parameters. Age, BMI, Duration, FBG, HBA1C, IN, IR, and IS are not significant in control and type 2 diabetic maltose, as shown in Table 1.

Table 1: differences of biomarkers in study subjects according to diet control.

Diet Control	**Control**		**P**	**DM2**		**P**
	Yes	No		Yes	No	
Age	36.86±2.72	30.33±3.06	0.188	45.50±2.43	51.00±1.73	0.064
BMI(KG/M2)	28.00±1.07	28.30±1.698	0.918	29.90±1.053	28.41±0.842	0.273
Duration	-	-	-	4.407±1.25	6.923±0.90	0.100
FBG(mg/dl)	96.06±3.44	92.86±3.918	0.570	199.20±23.25	227.83±17.12	0.316
HBA1C%	5.33±0.013	5.07±0.081	0.285	8.96±0.54	9.040±0.418	0.913
IN(µIU/ml)	2.40±0.271	2.73±0.243	0.356	4.597±0.45	4.002±0.520	0.424
IR(mcu/ml)	0.56±0.06	0.62±0.063	0.494	1.90±0.20	2.102±0.29	0.609
IS	0.44±0.014	0.415±0.006	0.129	0.61±0.070	0.603±0.06	0.910

Differences in biomarkers in study subjects according to family history.

In these studies, the statistical analysis elucidates all parameters. Age (0.139), BMI (0.965), Duration, FBG (0.669), HBA1C (0.979), IN (0.979), and IR (0.794) are not significant while (IS) (0.049) is significant, but in diabetic maltose type 2, the insulin sensitivity (IS) (0.005) is significant. whilst the age (0.088), BMI (0.501), duration (0.356), FBG (0.214), duration (0.356) and insulin resistance (0.408) are not significant **($p<0.05$)** as shown in table 2.

Table 2: differences of biomarkers in study subjects according to family history.

	Yes	No		Yes	No	
Age	41.00±7.44	31.88±2.07	0.139	50.75±1.768	45.65±2.424	0.088
BMI(KG/M2)	28.18±1.17	28.05±1.132	0.965	28.65±0.80	29.57±1.154	0.501
Duration		-		6.466±1.00	5.033±1.105	0.356
FBG(mg/dl)	97.25±6.39	93.92±2.84	0.669	230.05±17.92	194.39±21.50	0.214
HBA1C%	5.150±0.217	5.14±0.07	0.979	9.377±0.451	8.41±0.445	0.159
IN(µIU/ml)	2.395±0.516	2.586±0.197	0.979	4.349±0.491	4.064±0.521	0.704
IR(mcu/ml)	0.55±0.11	0.59±0.049	0.794	2.148±0.25	1.81±0.29	0.408
IS	0.468±0.038	0.421±0.007	0.049	0.707±0.063	0.448±0.047	0.005

Differences of biomarkers in study subjects according to physical activity .
Results of statistical analysis of this study showed all parameters (age, BMI, duration, FBG, HBA1C, IN, IR, and IS) are nonsignificant in control and patients ($p<0.05$), as shown in table 3.

Table 3: differences of biomarkers in study subjects according to physical activity.

Physical Activity	**Control**		**P**	**DM2**		**P**
	Yes	No		Yes	No	
Age	34.75±3.633	32.50±2.54	0.640	46.71±1.98	51.178±2.09	0.182
BMI(KG/M2)	29.02±	27.72±0.85	0.571	28.83±0.95	29.21±0.981	0.775
Duration	-	-		5.519±1.02	6.37±1.104	0.574
FBG(mg/dl)	96.06±3.44	94.818±2.611	0.777	217.46±20.39	215.14±18.79	0.934
HBA1C%	5.33±0.103	5.145±0.079	0.998	9.139±0.505	8.86±0.415	0.679
IN(µIU/ml)	2.40±0.271	2.49±0.216	0.582	4.697±0.47	3.717±0.54	0.177
IR(mcu/ml)	0.56±0.06	0.58±0.053	0.728	2.341±0.27	1.65±0.254	0.074
IS	0.44±0.014	0.42±0.009	0.897	0.618±0.06	0.595±0.06	0.807

differences in biomarkers in study subjects according to diet control.
Results of statistical analysis elucidate all parameters. Age, BMI, Duration, FBG, HBA1C, IN, IR, and IS are not significant in control and type 2 diabetic maltose, as shown in Table 4.

Table 4: differences of biomarkers in study subjects according to diet control.

Diet Control	**Control**		**P**	**DM2**		**P**
	Yes	No		Yes	No	
Age	36.86±2.72	30.33±3.06	0.188	45.50±2.43	51.00±1.73	0.064
BMI(KG/M2)	28.00±1.07	28.30±1.698	0.918	29.90±1.053	28.41±0.842	0.273
Duration	-	-	-	4.407±1.25	6.923±0.90	0.100
FBG(mg/dl)	96.06±3.44	92.86±3.918	0.570	199.20±23.25	227.83±17.12	0.316
HBA1C%	5.33±0.013	5.07±0.081	0.285	8.96±0.54	9.040±0.418	0.913
IN(µIU/ml)	2.40±0.271	2.73±0.243	0.356	4.597±0.45	4.002±0.520	0.424
IR(mcu/ml)	0.56±0.06	0.62±0.063	0.494	1.90±0.20	2.102±0.29	0.609
IS	0.44±0.014	0.415±0.006	0.129	0.61±0.070	0.603±0.06	0.910

Single Locus Association Test (Binary phenotype):
Alleles:
The result of the statistical analysis of this study showed SNPrs10946398 (0.619) and SNPrs9356744 (0.962). The association between the two alleles is nonsignificant ($P<0.05$), and the fisher's p in SNPrs10946398 is phenotype carriers and in SNPrs9356744 is risk phenotype carriers.

Table 5: association between the two alleles rs10946398 and rs9356744

SNP	**Call rate**	**Chi^2**	**Pearson's p**	**Fisher's p**	**OR [95% CI]**	**Detail**		
rs10946398	0.877	0.246	0.619	0.681	0.814 [0.362~1.83]	Case Control	A 24(0.4) 18(0.45)	C 36(0.6) 22(0.55)
rs9356744	0.807	0.002	0.962	1	1.02 [0.436~2.383]	Case	C 27(0.465)	T

						Control	31(0.534) 16(0.47) 18(0.529)

the homologous alleles in SNP rs10946398 and heterologous alleles in SNP rs9356744 The result of the statistical analysis of this study is that the homologous alleles in SNP rs10946398 (0.725) and heterologous alleles in SNP rs9356744 (0.635) are nonsignificant in P<0.05, and these are phenotype carriers in both of SNPS

Table 6: the homologous alleles in SNP rs10946398 and heterologous alleles in SNP rs9356744

SNP	**Chi^2**	**Pearson's p**	**Fisher's p**	**Detail**			
rs10946398	0.123	0.725	0.775		A/A	C/C	
				Case	12(0.4)	18(0.6)	
				Control	9(0.45)	11(0.55)	
rs9356744	0.906	0.635	0.999		C/T	T/T	C/C
				Case	25(0.862)	3(0.103)	1(0.034)
				Control	16(0.941)	1(0.058)	0(0)

differences of biomarkers in study subjects according to SNP cdkrs10946398 genotypes
In these study the statistical analysis elucidates all parameters Age(0.561), Duration (0.097) , BMI(0.851), FBG(0.800), HBA1C(0.544), IN(0.140), IR(0.297), IS (0.497) no significant association between control (SNP)and patients **in(p<0.05)** as shown in table(8)

Table 7: differences of biomarkers in study subjects according to SNP cdkrs10946398 genotypes

Biomarkers	**Control (SNP109)**		**P**	**Patients**		**P**
	Aa	Cc		AA	CC	
Age	36.750±4.104	35.36±3.780	0.809	48.00±2.637	50.27±2.625	0.561
Duration				3.28±1.05	6.210±1.197	0.097
BMI(KG/M2)	26.99±0.968	28.47±2.380	0.619	29.137±0.972	29.44±1.162	0.851
FBG(mg/dl)	91.95±6.39	94.45±4.030	0.732	217.33±41.26	227.66±1 8.318	0.800
HbA1c%	5.02±0.119	5.27±0.081	0.089	8.415±0.576	8.812±0.361	0.544
IN µIU/ml)	3.202±0.519	2.121±0.317	0.078	5.401±0.722	3.767±0.733	0.140
IR(mcu/ml)	0.698±0.108	0.494±0.078	0.137	2.492±0.314	1.901±0.401	0.297
IS	0.416±0.012	0.429±0.013	0.509	0.426±0.083	0.377±0.017	0.497

differences of biomarkers in study subjects according to SNPcdkrs9356744 genotypes
In these study the statistical analysis association between SNP all parameters Age(0.304), Duration (0.487) , BMI(0.650), FBG(0.343), HBA1C(0.965), IN(0.108), IR(0.578) and IS (0.153) no significant association between control (SNP)and patients **in(p<0.05)** as shown in table(8).

Table 8: mean differences of biomarkers in study subjects according to SNP cdkrs9356744 genotypes

Biomarkers	**Control (SNP93)**			**Patients P**			
	CT	TT	P	CC	CT	TT	P
Age	37.66±3.23	24.00	0.084	62.00±	49.08±2.133	57.66±11.34	0.304
Duration				4.00±	5.38±1.29	10.00±2.88	0.487
BMI(KG/M2)	28.33±1.761	24.46	0.352	29.29±	30.42±1.159	27.25±1.372	0.650
FBG(mg/dl)	93.30±4.003	114.00	0.038	253.00±	207.08±16.09	291.66±117.94	0.343
HbA1c%	5.216±0.082	4.90	0.112	8.200±	8.67±0.384	8.80±1.39	0.965
IN	2.546±0.374	2.14	0.647	0.762±	4.47±0.551	1.48±0.964	0.108
IR(mcu/ml)	0.57±0.084	0.60	0.883	0.476±	2.00±0.280	1.62±1.396	0.578
IS	0.42±0.011	0.418	0.793	0.437±	0.369±0.012	0.44±0.073	0.153

DISCUSSION

Fasting Blood Glucose (FBG)

The results of this study showed no significantly elevation of FBG in the type 2 diabetic group than the control, and these no agreement with the study(9) Following the intervention, the acupressure group's serum FBS level dropped considerably more than that of the control group (p = 0.02).
Insulin sensitivity, insulin resistance, and insulin hormone

According to the study's findings, individuals with type 2 diabetes had nonsignificantly higher levels of the hormone insulin than those in the control group, but they did have higher amounts of the hormone. The current study's findings demonstrated that the patients with type 2 diabetes had significantly higher levels than the control group. These findings are consistent with the study of (10) that discovered that patients with type 2 diabetes had elevated insulin hormone levels, which were linked to the presence of insulin resistance.
Insulin resistance's effects The results of this investigation are consistent with the work of (11) and shown that the patients with type 2 diabetes had considerably greater levels than the control group. When a normal or high amount of insulin results in a diminished biological response, this is known as insulin resistance (12). This is traditionally used to describe decreased sensitivity to insulin-mediated glucose disposal (13).

Hemoglobin$_{A1c}$
These findings are inconsistent with the current study, which revealed that the type 2 diabetes patients had much lower levels than the control group. This indicates that there were significant differences ($0.001<P<0.025$) in the HBA1C levels of these four groups. While there were no significant connections between HBA1C and age, sex, or length of disease, there was a good link among the diabetic participants between HBA1C level and measures including fasting blood sugar, urine sugar, and degree of diabetes management. According to the results gathered, the HBA1C test can be used as an impartial gauge of glucose control in individuals with diabetes (14).

Body Mass Index (BMI)
According to the current study's findings, individuals with type 2 diabetes had nonsignificantly higher Body Mass Index (BMI) values than the control group, which is inconsistent with the findings. BMI has a nonlinear relationship with all-cause mortality in type 2 diabetes, with the overweight group—both male and female—having the lowest risk. To evaluate causation and sex differences and to elucidate the association with cardiovascular mortality, more study is required.(15)in the study(16). This study set out to investigate the relationship between body mass index (BMI) and the prevalence of dyslipidemia, hypertension, and diabetes mellitus. The outcome of these investigations Increased BMI was associated with increased prevalence of diabetes mellitus in these studies ($p < 0.001$). Over 75% of patients for each disease had a BMI of > 25 kg/m2.

Systolic and diastolic pressure (SY&DY)
The study's findings demonstrated that the type 2 diabetes group's systolic and diastolic blood pressure differed significantly from that of the control group. A retrospective cohort research found a correlation between systolic and diastolic blood pressure and all-cause mortality in individuals with recently diagnosed type 2 diabetes (17).
The use of elevated blood pressure as a marker for insulin resistance, a key characteristic of diabetes and cardiovascular disease, resulted from other studies showing a correlation between endothelial dysfunction and elevated blood pressure, which is linked to insulin resistance (18).
The statistical analysis of this study revealed SNPrs9356744 (0.962) and SNPrs10946398 (0.619). There is no agreement with the findings, and the two alleles' correlation is nonsignificant ($P<0.05$) (19).This indicates , cdkal1 polymorphisms' contribution to T2D risk appears to be correlated with BMI.
There is a very strong correlation between these, and they concur with the research of (20). Nominally significant associations between CDKAL1-rs10946398 and famine exposure during pregnancy were shown to increase the incidence of type 2 diabetes.
Additionally, the SNP rs9356744 is more prominent and significant in control.There is a very strong correlation between these, and they concur with the work of (21). Two polymorphisms in the CDKAL1 gene, rs7754840 (related with rs9356744, $r2 = 0.902$), were substantially connected to gestational diabetes mellitus (GDM) in the male population. Additionally, it was incorporated into a Japanese population's T2DM prediction model.

CDKAL1 association with Physiological parameter
The result of the statistical analysis of this study showed CDKAL1 elucidates all parameters Age, Duration , BMI , FBG, HBA1C, IN , IR, IS no significant association between control and patients **in($p<0.05$)** and these agreement with the study(22). the prevention of type 2 diabetes, irrespective of a person's genetic makeup (23). There were notable variations in BMI (kg/m2) between the participants and controls (all $p <.0001$). There was a statistically significant difference in CDKAL1 genotypes between T2DM and healthy controls ($p <.0001$). The role of cdkal1 polymorphisms in T2D risk appears to be related to sex, BMI, and HBA1C. (18)
In the state rs9356744 we found study that agreement with my result(24). a significant correlation ($P = 0.048$) between BMI and the rs9356744 genotypes (CC, CT, TT). Participants with the T allele of rs9356744 had a decreased incidence of type 2 diabetes after controlling for confounding variables such as age, sex, and body mass index For T2DM, the T allele of rs9356744 acted as a separate protective factor. Significant relationships were found between the risk of T2DM and rs9356744.

They found a recessive impact for type 2 diabetes at CDKAL1 (p DOMDEV = 5 × 10−4). In line with a prior research, homozygous risk allele carriers had an OR of 1.48 (95% CI 1.32, 1.65) compared to homozygous non-risk allele carriers, whereas the heterozygous group had an OR of 1.06 (95% CI 0.99, 1.14). No new connections with genome-wide significance were found by us (25).

Numerous genetic studies have examined the relationship between single nucleotide polymorphisms (SNPs) and type 2 diabetes mellitus (T2DM) in European, Asian, and African American populations (26) and in other research (18).It appears that sex is linked to the contribution of CDKAL1 polymorphisms to T2D risk. Poor glycemic control was more likely to occur in females with risk alleles of CDKAL1 variations linked to type 2 diabetes than in men.(27).

REFERENCES

1. Li L, Wang J, Ping Z, Li Y, Wang C, Shi Y, Zhou W, Zhang L. Interaction analysis of gene variants of TCF7L2 and body mass index and waist circumference on type 2 diabetes. Clinical Nutrition. 2020 Jan 1;39(1):192-7.
2. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsdottir T, Walters GB, Styrkarsdottir U, Gretarsdottir S, Emilsson V, Ghosh S, Baker A. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. Nature genetics. 2007 Jun;39(6):770-5.
3. Wei FY, Suzuki T, Watanabe S, Kimura S, Kaitsuka T, Fujimura A, Matsui H, Atta M, Michiue H, Fontecave M, Yamagata K. Deficit of tRNA Lys modification by Cdkal1 causes the development of type 2 diabetes in mice. The Journal of clinical investigation. 2011 Aug 15;121(9).
4. Takesue Y, Wei FY, Fukuda H, Tanoue Y, Yamamoto T, Chujo T, Shinojima N, Yano S, Morioka M, Mukasa A, Kuratsu J. Regulation of growth hormone biosynthesis by Cdk5 regulatory subunit associated protein 1-like 1 (CDKAL1) in pituitary adenomas. Endocrine Journal. 2019;66(9):807-16.
5. Ghosh C, Das N, Saha S, Kundu T, Sircar D, Roy P. Involvement of Cdkal1 in the etiology of type 2 diabetes mellitus and microvascular diabetic complications: a review. Journal of Diabetes & Metabolic Disorders. 2022 Jan 13:1-1.
6. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. science. 2007 Jun 1;316(5829):1341-5.
7. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007 Jun 1;316(5829):1331-6.
8. Li YY, Wang LS, Lu XZ, Yang ZJ, Wang XM, Zhou CW, Xu J, Qian Y, Chen AL. CDKAL1 gene rs7756992 A/G polymorphism and type 2 diabetes mellitus: a meta-analysis of 62,567 subjects. Scientific reports. 2013 Nov 4;3(1):3131.
9. Zarvasi A, Jaberi AA, Bonabi TN, Tashakori M. Effect of self-acupressure on fasting blood sugar (FBS) and insulin level in type 2 diabetes patients: a randomized clinical trial. Electronic physician. 2018 Aug;10(8):7155.
10. Fruci B, Giuliano S, Mazza A, Malaguarnera R, Belfiore A. Nonalcoholic fatty liver: a possible new target for type 2 diabetes prevention and treatment. International Journal of Molecular Sciences. 2013 Nov 20;14(11):22933-66.
11. Mazza, D., Bairstow, P., Buchan, H., Chakraborty, S. P., Van Hecke, O., Grech, C., & Kunnamo, I. (2013). Refining a taxonomy for guideline implementation: results of an exercise in abstract classification. Implementation Science, 8, 1-10.
12. Cefalu WT. Insulin resistance: cellular and clinical concepts. Experimental biology and medicine. 2001 Jan;226(1):13-26.
13. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinology and Metabolism Clinics. 2004 Jun 1;33(2):283-303.
14. Tze WJ, Thompson KH, Leichter J. HbAlc—an indicator of diabetic control. The Journal of pediatrics. 1978 Jul 1;93(1):13-6.
15. Zaccardi F, Dhalwani NN, Papamargaritis D, Webb DR, Murphy GJ, Davies MJ, Khunti K. Nonlinear association of BMI with all-cause and cardiovascular mortality in type 2 diabetes mellitus: a systematic review and meta-analysis of 414,587 participants in prospective studies. Diabetologia. 2017 Feb;60:240-8.
16. Bays HE, Chapman RH, Grandy S, SHIELD Investigators' Group. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. International journal of clinical practice. 2007 May;61(5):737-47.
17. Vamos EP, Harris M, Millett C, Pape UJ, Khunti K, Curcin V, Molokhia M, Majeed A. Association of systolic and diastolic blood pressure and all cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study. Bmj. 2012 Aug 30;345.

18. Laakso M, Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. Nature reviews endocrinology. 2014 May;10(5):293-302.
19. Tian Y, Xu J, Huang T, Cui J, Zhang W, Song W, Chen H, Huang P, Yang S, Wang L, He X. A novel polymorphism (rs35612982) in CDKAL1 is a risk factor of type 2 diabetes: a case-control study. Kidney and Blood Pressure Research. 2019 Oct 22;44(6):1313-26.
20. Song C, Ding C, Yuan F, Feng G, Ma Y, Liu A. Ten SNPs may affect type 2 diabetes risk in interaction with prenatal exposure to Chinese famine. Nutrients. 2020 Dec 18;12(12):3880.
21. Rosta K, Al-Aissa Z, Hadarits O, Harreiter J, Nádasdi Á, Kelemen F, Bancher-Todesca D, Komlósi Z, Németh L, Rigó Jr J, Sziller I. Association study with 77 SNPs confirms the robust role for the rs10830963/G of MTNR1B variant and identifies two novel associations in gestational diabetes mellitus development. PloS one. 2017 Jan 10;12(1):e0169781.
22. Verma AK, Beg MM, Khan NA, Goyal Y, Dev K, Joshi PC. CDKAL1 (rs10946398) and TCF7L2 (rs7903146) gene polymorphisms and their association with risk of type-2 diabetes mellitus in population of Uttarakhand, India. Meta Gene. 2020 Dec 1;26:100767.
23. Schnurr TM, Jakupović H, Carrasquilla GD, Ängquist L, Grarup N, Sørensen TI, Tjønneland A, Overvad K, Pedersen O, Hansen T, Kilpeläinen TO. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. Diabetologia. 2020 Jul;63:1324-32.
24. Teng F, Qin R, Liu X, Geng H, Xu W, Wu T, Li Y, Lai P, Liang J. Interaction between the rs9356744 polymorphism and metabolic risk factors in relation to type 2 diabetes mellitus: The Cardiometabolic Risk in Chinese (CRC) Study. Journal of Diabetes and its Complications. 2021 Apr 1;35(4):107855.
25. Wood AR, Tyrrell J, Beaumont R, Jones SE, Tuke MA, Ruth KS, Yaghootkar H, Freathy RM, Murray A, Frayling TM, Weedon MN. Variants in the FTO and CDKAL1 loci have recessive effects on risk of obesity and type 2 diabetes, respectively. Diabetologia. 2016 Jun;59(6):1214-21.
26. Benberin VV, Vochshenkova TA, Abildinova GZ, Borovikova AV, Nagimtayeva AA. Search for polymorphic variants of genes associated with type 2 diabetes in individuals of the Kazakh population. Revista Turismo Estudos e Práticas-RTEP/UERN. 2020 Mar 1(2):1-0.
27. Lee HA, Park H, Hong YS. Sex differences in the effects of CDKAL1 variants on glycemic control in diabetic patients: findings from the Korean genome and epidemiology study. Diabetes & Metabolism Journal. 2022 Feb 8;46(6):879-89.
28. Naem AA, Al-Terehi MN, Ghafil FA, Ataya FS, Batiha GE, Alexiou A, Papadakis M, Welson NN, Hadi NR. The Influence of OCT3 and MATE2 Genetic Polymorphisms in Poor Response to Metformin in Type 2 Diabetes Mellitus. Endocrinology, Diabetes & Metabolism. 2024 Sep;7(5):e486.
29. Naem AA, Al-Terehi MN, Ghafil FA, Majeed S, Hadi NR, Al-Mudafer D. Influence of different factors (duration of disease, gender, education, patients' history, job and age) in metformin response in type 2 diabetes mellitus patient. Wiadomosci lekarskie (Warsaw, Poland: 1960). 2024;77(7):1356-63.
30. Naem AA, Ghafil FA, Al-Terehi MN, Majeed S, Al-Mudafer D, Hadi NR. Diet control and BMI impact on Metformin response in type 2 Diabetes mellitus patients. Wiad Lek. 2024;77(8):1575-81.
31. Ahmed SS. A study to evaluate platelet parameters in patients with type 2 diabetes mellitus: A case-control study. Medical Journal of Babylon. 2024 Jan 1;21(1):124-8.
32. Al-Saidy EA, Al-Ali ZA. Evaluation of osteocalcin and reproductive hormones in men with type 2 diabetes in Misan province/Iraq. Medical Journal of Babylon. 2020 Apr 1;17(2):126-32.
33. Al-Musawi HS, Jawad MA, Al-Terehi MN, Kadhim AJ. X-ray Repair Cross-complementing Group 1 (Arg399Gln) Genotyping in Diabetes Mellitus Type 2 with Hypertension. International Journal of Pharmaceutical Quality Assurance. 2021;12(3):249-252.
34. Al-Hassan FA, Al-Musawi HS. Poor control of oxidative stress index is associated with increased DNA methylation in retinopathy patients of a sample from babylonian population. Med J Babylon 2024;21:149-54.
35. Hawraa Sabah Al-Musawi, Makarim Qassim Al-Lami and Ali H. Al-Saadi (2021) Age and gender impact on glycaemic control, renal function and oxidative stress parameters in Iraqi patients type 2 diabetes mellitus. Biochem.Cell. Arch. 21, 491-499. DocID: https://connectjournals.com/03896.2021.21.491