

ALLELE AND GENOTYPE FREQUENCIES OF THE *CDKAL1* rs7754840 G>C POLYMORPHISM IN TURKISH HEALTHY INDIVIDUALS: A POPULATION-BASED STUDY

TÜRK SAĞLIKLI BİREYLERDE *CDKAL1* rs7754840 G>C POLİMORFİZMİNİN ALEL VE GENOTİP SIKLIKLARI: POPÜLASYON TEMELLİ BİR ÇALIŞMA

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ABSTRACT

Objective: The *CDKAL1* rs7754840 G>C polymorphism is link to defective insulin release and an elevated risk of type 2 diabetes mellitus. The objective of the current research was to identify the frequencies of alleles and genotypes for the rs7754840 G>C polymorphism in healthy Turkish individuals and to contrast them with those observed in other populations. The findings were also discussed based on previous research about its role in diabetes risk and treatment response.

Material and Method: The *CDKAL1* rs7754840 polymorphism was examined in DNA samples obtained from 112 healthy Turkish subjects through polymerase chain reaction and restriction fragment length polymorphism process. Allele and genotype frequencies were assessed and statistically compared with data from diverse populations.

Result and Discussion: Genotype analysis revealed frequencies of 7.1% for homozygous variant, 40.2% for heterozygous, and 52.7% for homozygous wild-type, corresponding to allele frequencies of 27.2% (variant) and 72.8% (wild-type). The frequencies of the *CDKAL1* rs7754840 variant allele were consistent with those determined in American, non-Finnish European, South Asian, and most East Asian populations ($p>0.05$). However, the variant allele frequency differed significantly from that reported in populations of Black ancestry. In conclusion, the present research offers current data on the frequency of the *CDKAL1* rs7754840 variant in healthy Turkish individuals. Genotype and allele frequencies were observed to be significantly distinct between the Turkish population and several other ethnic groups. These findings may contribute to future research in genetic epidemiology, pharmacogenetics, and personalized medicine.

Keywords: *CDKAL1*, polymorphism, rs7754840, Turkish population

ÖZ

Amaç: *CDKAL1* rs7754840 G>C polimorfizmi, kusurlu insülin salınımı ve tip 2 diyabet riskinin artmasıyla bağlantılıdır. Bu araştırmanın amacı, sağlıklı Türk bireylerde rs7754840 G>C polimorfizminin alel ve genotip sıklıklarını belirlemek ve bunları diğer popülasyonlarda gözlenen sıklıklarla karşılaştırmaktır. Bulgular ayrıca, diyabet riski ve tedavi yanıtı üzerindeki rolü hakkındaki önceki araştırmalara dayanarak tartışılmıştır.

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Gereç ve Yöntem: *CDKAL1* rs7754840 polimorfizmi, 112 sağlıklı Türk bireyden alınan DNA örneklerinde polimeraz zincir reaksiyonu ve restriksiyon fragman uzunluk polimorfizmi yöntemiyle incelendi. Alel ve genotip sıklıkları değerlendirildi ve farklı popülasyonlardan elde edilen verilerle istatistiksel olarak karşılaştırıldı.

Sonuç ve Tartışma: Genotip analizinde homozigot varyant için %7.1, heterozigot için %40.2 ve homozigot yabanıl tip için %52.7 sıklıkları belirlendi; bu da %27.2 (varyant) ve %72.8 (yabanıl tip) alel sıklıklarına karşılık geliyordu. *CDKAL1* rs7754840 varyant alelinin sıklıkları, Amerikan, Finli olmayan Avrupalı, Güney Asyalı ve çoğu Doğu Asyalı popülasyonda belirlenen sıklıklarla tutarlıydı ($p > 0,05$). Ancak, varyant alel sıklığı Afrika kökenli popülasyonlarda bildirilen sıklıktan önemli ölçüde farklıydı. Sonuç olarak, bu araştırma sağlıklı Türk bireylerinde *CDKAL1* rs7754840 varyantının sıklığı hakkında güncel veriler sunmaktadır. Türk popülasyonu ile diğer bazı etnik gruplar arasında genotip ve alel frekanslarının önemli ölçüde farklı olduğu gözlemlendi. Bu bulguların genetik epidemiyoloji, farmakogenetik ve kişiselleştirilmiş tıp alanındaki gelecekteki araştırmalara katkı sağlayabilir.

Anahtar Kelimeler: *CDKAL1*, polimorfizm, rs7754840, Türk popülasyonu

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a health issue of world-wide significance that causes a serious threat to public health and national economies, with its prevalence continuing to rise in numerous countries that include Türkiye. The International Diabetes Federation (IDF) predicts that in 2024, there are roughly 9.6 million adults between the ages of 20 and 79 with diabetes in Türkiye and that this figure is expected to rise to 14.1 million in the same age group by 2050 [1].

Although the molecular mechanisms contributing to the development of T2DM have not been completely elucidated, it is thought that a combination of various environmental and genetic elements plays a part in the pathogenesis of the disease [2]. Along with the significant part of environmental determinants such as diet and lifestyle, genetic factors are also recognized as a key contributor to T2DM susceptibility [3,4]. In the last few years, numerous genes related to T2DM have been detected in genome-wide association studies (GWAS) [2]. Of these, the cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like (*CDKAL1*) gene has been determined as one of the genes strongly linked to T2DM in GWAS [5]. The *CDKAL1* gene, spanning 697,947 bp [6], codes for a 65-kDa protein and is situated at chromosome 6p22.34 that has been linked to beta-cell dysfunction and a higher susceptibility to T2DM [7]. *CDKAL1* contributes to β -cell function via the suppression of CDK5 activity [5]. Risk variants of *CDKAL1* gene may impair its normal function, leading to defective insulin secretion [8,9]. Among *CDKAL1* variants, the rs7754840 G-to-C polymorphism is the most frequently observed [10]. The *CDKAL1* rs7754840 polymorphism has been documented to be connection not only to disease risk but also to the response to antidiabetic drugs [2,5,11-14].

The frequencies of alleles and genotypes for the *CDKAL1* rs7754840 polymorphism have been investigated across various populations. Although several investigations have studied the relationship between disease states and the aforementioned polymorphism in Turkish populations, data regarding its frequency in healthy individuals remain limited [10,15]. Previous studies in the Turkish population primarily focused on disease-specific cohorts, whereas the present study exclusively includes healthy Turkish individuals [10,15]. This study provides population-based allele and genotype frequency data for *CDKAL1* rs7754840 in a healthy Turkish population and offers a broader global comparison of these findings using 1000 Genomes Project data [16].

The objective of the research was to assess the frequencies of allele and genotype for the *CDKAL1* rs7754840 polymorphism in healthy Turkish individuals and to compare these findings with those reported in various ethnic and geographic populations using Phase 3 data from the 1000 Genomes Project Consortium [16]. Identifying genetic differences between populations may facilitate improved insight into disease risks and the development of personalized treatment approaches. In addition, the results were considered in the context of pharmacogenetic and clinical relevance, with reference to their possible associations with type 2 diabetes susceptibility and treatment response as reported in previous studies.

MATERIAL AND METHOD

Samples

The DNA samples analyzed in this research were partially derived from samples extracted during previous research (22/10/2015, reference number: 2015/317). DNA yields were determined by measuring absorbance at 260 nm (A260) using a NanoDrop spectrophotometer. The Mersin University Ethics Committee allowed ethical approval for the current research (02/09/2020, reference number: 2020/614). A total of 112 unrelated, healthy Turkish volunteers aged between 18 and 65 years were included, and this research was executed in compliance with Good Clinical Practice standards and the ethical framework of the Declaration of Helsinki.

Genotyping

Analysis of the rs7754840 polymorphism was brought about based on the technique indicated by Soltani et al. [5] with minor revisions. The polymorphism at issue was amplified via PCR employing 5'-TCTTGAGTAGTCACCTGGTCA-3' as the forward primer and 5'-AAAAATCCTCGCAACAACAGA-3' as reverse primers. PCR was executed in a total volume of 20- μ l that contains 1.5 mM MgCl₂, 1.50 units of Taq polymerase (Fermentas), 0.2 mM each deoxynucleotide triphosphate (Fermentase), 10 x PCR buffer, 300-500 ng genomic DNA on a MiniAmp Plus Thermal Cycler (Thermo Fisher Scientific, USA). The PCR experiment started with a primary denaturation step for 5 minutes at 95 °C, and carried on 35 cycles of 94 °C for 50 seconds, 58 °C for 50 seconds, and 72 °C for 50 seconds, with the last elongation step at 72 °C for 5 minutes. A DNA-free negative control was incorporated in all PCR experiments to confirm that reaction components were uncontaminated. Electrophoretic separation of PCR products was performed on a 1.0% agarose gel with ethidium bromide (EtBr, 500 ng/ml) to ensure visibility. To perform RFLP assay, a 10- μ l aliquot of the PCR sample was incubated using FastDigest Tail restriction enzyme (Thermo Scientific™) at 65°C for 15 minutes in a total volume of 20- μ l, adjusted with a suitable buffer. A 2.0% agarose gel with EtBr was employed to analyze the segments. The wild-type genotype (GG) was represented by a single band of 781 bp. The variant genotype (CC) was cleaved into fragments of 495 and 286 bp, whereas the heterozygous genotype (GC) was digested into fragments of 781, 495 and 286 bp. Quality assurance was performed by randomly reanalyzing 10% of the samples, which showed full compliance.

Statistical Analysis

The frequencies of alleles and genotypes were assessed by the genotype counting method. Comparisons between observed and expected frequencies of the *CDKAL1* rs7754840 G>C polymorphism were assessed by the chi-square test (χ^2) according to the Hardy-Weinberg equilibrium. The findings from the current research were contrasted with earlier published data from several populations. Frequency differences among populations were evaluated using the χ^2 test. A *P* value below 0.05 was deemed markedly significant. Analysis of the findings obtained from the study was executed with IBM SPSS Statistics version 25.0 for Windows.

RESULT AND DISCUSSION

CDKAL1 rs7754840 G>C polymorphism was analyzed in DNA samples of 112 healthy Turkish subjects. Of the 112 individuals involved in the study, 58 (52 %) were female, 54 (48 %) were male. Participants had a mean age of 28.45 ± 9.59 years (mean $\pm$ standard deviation).

The frequencies of the homozygous variant, homozygous wild-type, and heterozygous genotypes were 7.1%, 52.7%, and 40.2%, in the same order and accordingly, the allele frequencies for variant and wild-type were assessed as 27.2% and 72.8%, in the same order (Table 1). In addition, the observed genotype frequencies conform to the Hardy-Weinberg equilibrium ($\chi^2 = 0.02$, $p > 0.05$).

Table 1. The frequencies of *CDKAL1* rs7754840 G>C polymorphism in healthy Turkish subjects

Genotypes	Observed, n	Frequencies of Genotypes, %	Expected, n	Frequencies of Alleles, %
Wild-type (GG)	59	52.7	59.3	Wild-type (G): 72.8 Variant (C): 27.2 $df = 1$ $\chi^2: 0.02, p > 0.05$
Heterozygous variant (GC)	45	40.2	44.4	
Homozygous variant (CC)	8	7.1	8.3	
Total	112	100	112	

Figure 1 displays agarose gel images of polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) products of *CDKAL1* rs7754840 G>C polymorphism detected using electrophoresis.

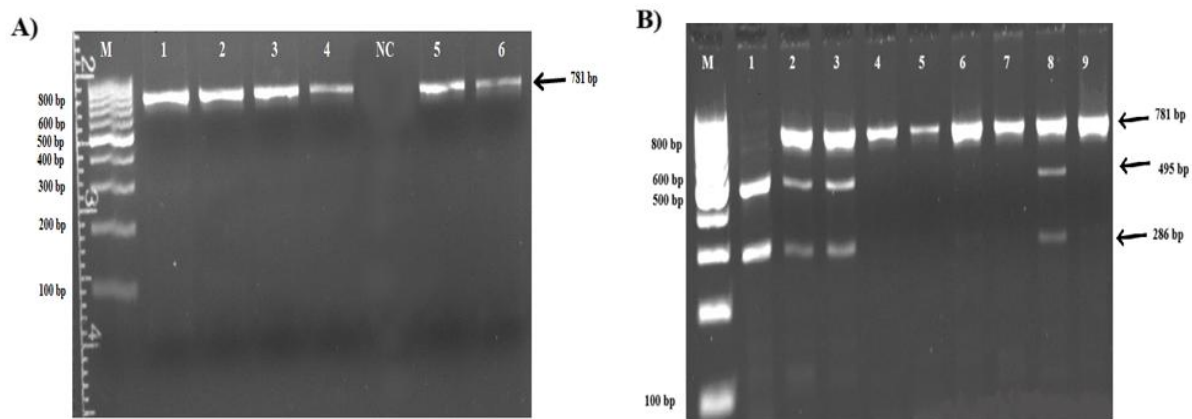


Figure 1. Agarose gel images illustrating the *CDKAL1* rs7754840 G>C polymorphism identified by (A) polymerase chain reaction (PCR) and (B) restriction fragment length polymorphism (RFLP). For A (PCR) part; Lane 1-6: PCR product (781 bp), Lane M: 100 bp DNA ladder (GeneRuler™ 100 bp DNA Ladder, Thermo Scientific™), Lane NC: negative control. For B (RFLP) part; Lane 1: homozygous variant genotype (495, 286 bp), Lane 2, 3 and 8: heterozygous variant genotype (781, 495, 286 bp), Lane 4-7, 9: wild-type genotype (781bp), Lane M: 100 bp DNA Ladder (GeneRuler™ 100 bp DNA Ladder, Thermo Scientific™)

This study explored the frequencies of genotype and allele for the rs7754840 polymorphism in healthy subjects from the Turkish population, with the mutant allele (C) frequency found to be 27.2%. The findings provide valuable data on the distribution of this variant in the Turkish population and contribute to the limited research on its genetic profile in healthy individuals from Türkiye. In a study by Helvacı et al., the impact of single-gene polymorphisms in *CDKAL1* rs7754840 and *TCF7L2* rs7903146 on the development of new-onset diabetes after kidney transplant recipients was investigated [10]. For the *CDKAL1* rs7754840 polymorphism, they reported genotype frequencies of 46.9% for heterozygous, 45.2% for the wild-type, and 7.9% for mutant genotypes, with allele frequencies of 68.6% for the wild-type and 31.4% for the mutant. In the study by Arikoglu et al., the influence of genes strongly associated with T2DM in GWAS, including *CDKAL1* (rs10946398 A/C and rs7754840 G/C), *MTNR1B*, *ADAMTS9*, *ENPP1*, and *THADA* on T2DM and its characteristic traits was examined in a sample of 824 Turkish individuals, consisting of nonobese T2DM patients and nonobese healthy controls [15]. Regarding the *CDKAL1* rs7754840 polymorphism, they reported genotype frequencies among the healthy controls as 16.0% for the heterozygous, 82.7% for the wild-type, and 1.3% for the mutant genotypes, with allele frequencies of 91.0% for the wild-type and 9.0% for the mutant. Our results are consistent with those of Helvacı et al. but differ significantly from Arikoglu et al. [10,15]. These differences may be due to variations in sample characteristics (non-obese individuals, T2DM, or

the general healthy population, *etc.*), sample size, environmental factors, and regional genetic diversity. Accordingly, these findings should be interpreted in a contextual and descriptive manner, rather than as direct comparisons of allele and genotype frequencies.

In this research, the frequencies of allele and genotype for the *CDKALI* rs7754840 polymorphism were compared with those reported in various ethnic and geographic populations using Phase 3 data from the 1000 Genomes Project Consortium, accessed via the Ensembl Genome Browser (Table 2, Table 3) [16,17]. The findings reveal that this genetic variant shows significant differences among certain populations. The allele and genotype frequencies used for comparative analyses were obtained from Phase 3 data of the 1000 Genomes Project, which include approximately 2.500 individuals from 26 populations generated using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping approaches. This dataset defines the distribution of genetic variation in a global sample and allows interpretation of allele frequency differences between the Turkish population and various ethnic and geographic populations [16]. The present findings reveal that the genetic variant at issue shows significant differences among certain populations.

Table 2. Distribution of the frequencies of alleles and genotypes for *CDKALI* rs7754840 G>C polymorphism in diverse populations (White ancestry)

Ancestry	Population	Number of Subjects	Frequencies of Genotypes, n (%)			Frequencies of Alleles, n (%)		References
		N	GG	GC	CC	G	C	
White								
European	Turkish	112	59 (52.7)	45 (40.2)	8 (7.1)	163 (72.8)	61 (27.2)	The current study
	Turkish	239	108 (45.2)	112 (46.9)	19 (7.9)	328 (68.6)	150 (31.4)	[10]
	Turkish	231	191 (82.7)	37 (16.0)	3 (1.3)	419 (91.0)	43 (9.0) ^a	[15]
	Finnish in Finland (FIN)	99	35 (35.4)	48 (48.5)	16 (16.2)	118 (59.6)	80 (40.4) ^b	[16]
	Utah residents with Northern and Western European ancestry (CEU)	99	46 (46.5)	43 (43.4)	10 (10.1)	135 (68.2)	63 (31.8)	[16]
	Iberian populations in Spain (IBS)	107	53 (49.5)	40 (37.4)	14 (13.1)	146 (68.2)	68 (31.8)	[16]
	Tosceni in Italy (TSI)	107	59 (55.1)	38 (35.5)	10 (9.3)	156 (72.9)	58 (27.1)	[16]
American	Mexican Ancestry in Los Angeles, California (MXL)	64	29 (45.3)	29 (45.3)	6 (9.4)	87 (68.0)	41 (32.0)	[16]
	Colombian in Medellin, Colombia (CLM)	94	43 (45.7)	45 (47.9)	6 (6.4)	131 (69.7)	57 (30.3)	[16]
	Puerto Rican in Puerto Rico (PUR)	104	44 (42.3)	47 (45.2)	13 (12.5)	135 (64.9)	73 (35.1)	[16]
	Peruvian in Lima, Peru (PEL)	85	39 (45.9)	42 (49.4)	4 (4.7)	120 (70.6)	50 (29.4)	[16]

Frequency differences were assessed by χ^2 test. Significant at ^a $p < 0.001$ and ^b $p < 0.05$ in comparison with the findings of the present investigation. n: total number of subjects

In the present study, *CDKALI* rs7754840 G>C variant frequencies are similar to White ancestry with variant allele frequencies between 27.1 % and 35.1%, comprising Iberian populations in Spain (IBS), Utah residents with Northern and Western European ancestry (CEU), Toscani in Italy (TSI), Colombian in Medellin, Colombia (CLM), Puerto Rican in Puerto Rico (PUR), Mexican Ancestry in Los Angeles, California (MXL) and Peruvian in Lima, Peru (PEL). However, it is statistically different

from Finnish in Finland (FIN) variant frequencies (40.4%) (Table 2). In Table 3, similarly, there was no statistically significant distinction between Turkish and South Asian populations that include Gujarati Indians in Houston, Texas, USA (GIH), Punjabi in Lahore, Pakistan (PJI), Bengali in Bangladesh (BEB), Sri Lanka Tamil in the United Kingdom (STU) and Indian Telugu in the United Kingdom (ITU) populations. The variant allele frequencies in South Asian populations were between 21.1 % and 35.5%. Conversely, markedly significant distinction were observed between the Turkish population and most East Asian populations, including Han Chinese in Beijing, China (CHB), Kinh in Ho Chi Minh City, Vietnam (KHV) and Japanese in Tokyo, Japan (JPT), while no significant differences were determined in Southern Han Chinese, China (CHS) and Chinese Dai in Xishuangbanna, China (CDX). Additionally, significant differences were found between the Turkish population and Black ancestry that include Esan in Nigeria (ESN), Luhya in Webuye, Kenya (LWK), African Caribbeans in Barbados (ACB), African ancestry in Southwest USA (ASW), Yoruba in Ibadan, Nigeria (YRI), Mende in Sierra Leone (MSL), Gambian in Western Division, The Gambia (GWD), regarding *CDKAL1* rs7754840 G>C polymorphism. The frequencies of the variant allele in these populations ranged from 54.9% to 73.5%.

As seen in Table 2 and Table 3, the *CDKAL1* rs7754840 variant shows different frequencies across populations (e.g., 9–31.4% in the Turkish population, 27.1–40.4% in European populations). This differences contribute to genetic variation at both intra- and inter-population levels. Since this variant is particularly associated with T2DM, the increased disease risk in rs7754840 carriers may lead to differences in susceptibility both within and between populations.

Table 3. Distribution of the frequencies of alleles and genotypes for *CDKAL1* rs7754840 G>C polymorphism in diverse populations (Asian and Black ancestry)

Ancestry	Population	Number of subjects	Frequencies of genotypes, n (%)			Frequencies of alleles, n (%)		References
		n	GG	GC	CC	G	C	
Asians								
South Asian	Punjabi in Lahore, Pakistan (PJI)	96	54 (56.2)	37 (38.5)	5 (5.2)	145 (75.5)	47 (24.5)	[16]
	Bengali in Bangladesh (BEB)	86	34 (39.5)	43 (50.0)	9 (10.5)	111 (64.5)	61 (35.5)	[16]
	Sri Lankan Tamil in the United Kingdom (STU)	102	66 (64.7)	29 (28.4)	7 (6.9)	161 (78.9)	43 (21.1)	[16]
	Indian Telugu in the United Kingdom (ITU)	102	56 (54.9)	42 (41.2)	4 (3.9)	154 (75.5)	50 (24.5)	[16]
	Gujarati Indians in Houston, Texas, USA (GIH)	103	59 (57.3)	39 (37.9)	5 (4.9)	157 (76.2)	49 (23.8)	[16]
East Asian	Chinese Dai in Xishuangbanna, China (CDX)	93	39 (41.9)	39 (41.9)	15 (16.1)	117 (62.9)	69 (37.1)	[16]
	Southern Han Chinese, China (CHS)	105	41 (39.0)	49 (46.7)	15 (14.3)	131 (62.4)	79 (37.6)	[16]
	Kinh in Ho Chi Minh City, Vietnam (KHV)	99	35 (35.4)	42 (42.4)	22 (22.2)	112 (56.6)	86 (43.4) ^a	[16]
	Han Chinese in Beijing, China (CHB)	103	33 (32.0)	55 (53.4)	15 (14.6)	121 (58.7)	85 (41.3) ^a	[16]
	Japanese in Tokyo, Japan (JPT)	104	35 (33.7)	53 (51.0)	16 (15.4)	123 (59.1)	85 (40.9) ^a	[16]

Table 3 (continue). Distribution of the frequencies of alleles and genotypes for CDKAL1 rs7754840 G>C polymorphism in diverse populations (Asian and Black ancestry)

Ancestry	Population	Number of Subjects n	Frequencies of Genotypes, n (%)			Frequencies of Alleles, n (%)		References
			GG	GC	CC	G	C	
Black								
African	Mende in Sierra Leone (MSL)	85	7 (8.2)	31 (36.5)	47 (55.3)	45 (26.5)	125 (73.5) ^b	[16]
	African Ancestry in Southwest USA (ASW)	61	10 (16.4)	35 (57.4)	16 (26.2)	55 (45.1)	67 (54.9) ^b	[16]
	Luhya in Webuye, Kenya (LWK)	99	15 (15.2)	48 (48.5)	36 (36.4)	78 (39.4)	120 (60.6) ^b	[16]
	Esan in Nigeria (ESN)	99	14 (14.1)	51 (51.5)	34 (34.3)	79 (39.9)	119 (60.1) ^b	[16]
	Gambian in Western Division, The Gambia (GWD)	113	15 (13.3)	54 (47.8)	44 (38.9)	84 (37.2)	142 (62.8) ^b	[16]
	Yoruba in Ibadan, Nigeria (YRI)	108	13 (12.0)	46 (42.6)	49 (45.4)	72 (33.3)	144 (66.7) ^b	[16]
	African Caribbeans in Barbados (ACB)	96	15 (15.6)	44 (45.8)	37 (38.5)	74 (38.5)	118 (61.5) ^b	[16]

Frequency differences were assessed by χ^2 test. Significant at ^a $p < 0.01$ and ^b $p < 0.001$ in comparison with the findings of the present investigation. n: total number of subjects

In the research performed by Stancáková et al., it was reported that in study 1, (the EUGENE2 cross-sectional study), which included subjects from Denmark, Finland, Germany, Italy, and Sweden, subjects with the CC and GC genotypes had 24% and 11% lower first-phase insulin secretion in comparison with subjects who had the GG genotype on intravenous glucose tolerance test ($p = 0.002$), respectively, and the allele C was relationship with more elevated glucose area under the curve in an oral glucose tolerance test ($p = 0.016$) [12]. Also, in study 2 (the ongoing prospective study of Finnish men), they declared that the rs7754840 polymorphism was significantly associated with T2DM and markers of impaired insulin release in the subjects who have normal glucose tolerance [12]. Correspondingly, Naser et al. reported an association between T2DM and the CDKAL1 rs7754840 variant in an Iraqi population [18]. Subjects with the GC and CC genotypes were reported to have a 2- and 3-fold increased risk, respectively, compared to those with the GG genotype in terms of developing T2DM. The mentioned polymorphism was reported to markedly elevate the risk of developing T2DM in the Iraqi population and substantially influence levels of insulin in these patients. Furthermore, in the study by Mansoori et al., the rs7754840 variant was determined to be related to T2DM in the Iranian population [2]. The C allele was more frequent in diabetic individuals, and those who had the CC genotype had a greater predisposition to the disease, while the GC genotype appeared to have a protective effect. The outcomes obtained suggest that the variant in question may affect the risk of diabetes. A comprehensive meta-analysis by Tuerxunyiming et al. evaluating the link between T2DM and the rs7754840 polymorphism, data from 70,141 individuals across 32 studies were examined [11]. The C allele was significantly linked to an elevated risk of diabetes across various genetic models, supporting the impact of the rs7754840 polymorphism in the development of T2DM. Overall, these studies demonstrate that the CDKAL1 rs7754840 variant can contribute to determining T2DM risk, early diagnosis, and the development of T2DM.

Genetic polymorphisms not only contribute to disease pathogenesis and individual susceptibility, but also serve as an important genetic determinant that affects drug response, thereby supporting the development of personalized therapeutic strategies. The CDKAL1 rs7754840 polymorphism not only affects disease risk but also serves as an important genetic determinant influencing drug response.

Osada et al. examined *CDKAL1* rs7754840 G>C polymorphism and therapeutic response to antidiabetic drugs in subjects with T2DM in a Japanese population [13]. For this polymorphism, the reduction in hemoglobin A1c (HbA1c) was significantly higher in subjects with the risk allele ($p=0.02$; CC -0.8%, CG -0.5%, GG -0.4%) after 3 months of dipeptidyl peptidase 4 inhibitors (DPP-4) use. For rs7754840, linear regression analysis also indicated that the reductions in HbA1c for each allele were -0.10% ($p=0.02$) following adjusting of covariates. These findings indicated that the polymorphism at this locus was in relationship with therapeutic DPP-4 blockers. In another study conducted in an Iranian population, Soltani et al. [5] found that the rs7754840 polymorphism significantly influenced the response to sulfonylurea therapy. The GG genotype was significantly associated with treatment resistance (odds ratio = 2.250 [95% confidential intervals: 1.010-5.012] $p=0.046$), and the allele G was found to be more frequent in individuals in the resistant group in comparison with the sensitive group. The CC and GC genotypes were in relationship with the sensitive phenotype and were more responsive to sulfonylurea therapy compared to the GG genotypes. Also, Qin et al. declared that in treatment-naïve patients who had T2DM in a Chinese population, patients carrying the genotype CG indicated a median HbA1c reduction of 1.44 (interquartile range, [IQR], 1.38–1.72) in the experimental group receiving sitagliptin combined with metformin, compared to 1.09 (IQR, 0.79–1.17) in the reference group receiving gliclazide combined with metformin ($p=0.053$) [14]. Overall, these studies demonstrate that the *CDKAL1* rs7754840 variant influences individual responses to antidiabetic drugs, supporting its potential role in personalizing T2DM treatment.

Briefly, genetic polymorphisms can give rise to discrepancies in predisposition to several illnesses, medicine efficacy and safety, and xenobiotic toxicity between and within populations [19].

This study has certain limitations. The differences observed in comparison with previous studies conducted in the Turkish population may be attributed to variations in cohort characteristics (e.g., healthy individuals versus patient groups) and variability in sample size. Accordingly, comparisons with earlier Turkish studies should not be regarded as direct frequency-based comparisons but rather as contextual and descriptive evaluations of population-level genetic variation. Furthermore, sampling structure, historical admixture, and demographic heterogeneity in both the Turkish population and the populations included in the 1000 Genomes Project can influence comparative analyses. Therefore, larger sample sizes and more regionally diverse studies are needed to validate these findings.

Despite these limitations, the data obtained from the study provide information on the frequency of the *CDKAL1* rs7754840 variant in healthy individuals in Türkiye. The findings reveal notable variations in the frequencies for allele and genotype of the *CDKAL1* gene between the Turkish population and other ethnic groups. These findings have the potential to contribute to studies in the fields of genetic epidemiology, pharmacogenetic analyses and personalized medicine strategies.

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AUTHOR CONTRIBUTIONS

Concept: Z.U.S.; Design: Z.U.S.; Control: Z.U.S.; Sources: Z.U.S.; Materials: Z.U.S.; Data Collection and/or Processing: Z.U.S.; Analysis and/or Interpretation: Z.U.S.; Literature Review: Z.U.S.; Manuscript Writing: Z.U.S.; Critical Review: Z.U.S.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

Approval for the study was received from the Mersin University Ethics Committee (02 September 2020, Reference Number: 2020/614). The DNA samples utilized in this study were derived from a previous project endorsed by the Mersin University Ethics Committee (22 October 2015, Reference Number: 2015/317). Written informed consent was received from all volunteers during blood collection.

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