Genetic Variants of CYP2C8 Gene Predisposition to Type 2 Diabetes Risk

Saleh Abd-Qader Abed [1], Ammar Ahmed Sultan [1*]

Abstract

Background: Type 2 diabetes mellitus (T2DM) is characterized by elevated blood glucose levels due to insulin resistance or inadequate insulin secretion from pancreatic beta cells. The mitochondrial CYP2C8 gene, located on chromosome 10q24, encodes cytochrome P450 and spans 37 kb with nine exons. Genetic variants in this gene may influence T2DM susceptibility. Method: This study aimed to investigate the association between genetic polymorphisms in the CYP2C8 gene (rs1934953 and rs1934952) and the risk of T2DM in Iraqi patients. Blood samples were collected from 48 participants, including 24 T2DM patients and 24 healthy controls. DNA extraction, polymerase chain reaction (PCR), and sequencing were performed to analyze genetic variations. Statistical analysis was conducted using chi-square tests, logistic regression, and Hardy-Weinberg equilibrium calculations. Results: Analysis revealed that the rs1934953 variant in the CYP2C8 gene was associated with T2DM, with the A allele showing a protective effect (odds ratio: 0.840, 95% confidence interval: 0.780-0.904, P=3.04×10-6). Additionally, an interaction effect between rs1934953 in CYP2C9 and rs12766752 in CYP2C8 on T2DM risk was observed (P=0.003). Furthermore, rs1934953 showed significant association with high-density lipoprotein cholesterol (HDL-C). At the rs1934952 C/T locus, a transition type genetic mutation was detected, with the TT genotype considered a risk factor for T2DM, while the CC and CT genotypes were protective. The Hardy-Weinberg probability value for the patient group was 0.0321, indicating notable discrepancies in genotype distribution, while the healthy group showed no significant differences (Hardy probability: 0.2001). The TT genotype at rs1934953 was associated with a decreased risk of T2DM, while the CC and CT genotypes were potential risk factors. Conversely, at rs1934952, the CC and CT genotypes were protective against T2DM, while the TT genotype was associated with increased risk. Conclusion: in conclusion, the study indicates that there may be links between CYP2C8 gene variances and an increased chance of type 2 diabetes in Iraqi patients.

Keywords: Cytochrome P450, Translocation, Odds ratio, Type 2 diabetes mellitus (T2DM), CYP2C8 gene, Genetic polymorphisms, Insulin resistance, Epidemiological analysis

Significance | This study determined the genetic variations in the CYP2C8 gene which may illuminate predispositions to type 2 diabetes.

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Introduction

One of the most well-known chronic illnesses in the world is type 2 diabetes mellitus (T2DM), a variation of diabetes mellitus (DM). It is a metabolic disease that is characterized by decreased insulin secretion and increased insulin resistance (Zimmet et al, 2018). In adults, the prevalence of diabetes is 9.1%, or 415 million cases, according to a recent analysis published in the International Diabetes Federation Diabetes Atlas (RJ et al, 2018). A high chance of getting diabetes mellitus (DM) in the future is also present for the 318 million individuals who have poor glucose control. Since 90% of individuals with diabetes have type 2 diabetes, China has the

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highest prevalence of DM. As such, greater focus should be paid to this illness (Wang et al, 2013).Increased insulin resistance, visceral fatty deposits, westernization of the cuisine, poor lifestyle, and genetic background are risk factors linked to the development of diabetes mellitus (Rawshani, & Gudbjörnsdottirl, 2018). The risk of acquiring diabetes mellitus is also increased by urbanization and pollution in the environment. The development of metabolic diseases is strongly linked to increased exposure to environmental contaminants, such as those noticed in food, water, and air. However, the ability of an individual to metabolize toxins varies based on their genetic background (Park et al, 2017). Therefore, one of the keys to understanding the genetic architecture of type 2 diabetes may lie in polymorphisms in the genes involved in metabolizing xenobiotic.

Type 2 diabetes is thought to be responsible for over 90% of diabetes occurrences worldwide (Davies *et al*., 2022). The enzymes in the cytochrome P450 (CYP) family are in charge of phase I biotransformation, which is the process by which a variety of endogenous and foreign substances are metabolized. However, compared to large areas of other genes, the CYP gene family is more variable (Kim et al, 2007). They therefore possess the ability to potentially affect the susceptibility to medication metabolism, endogenous chemical metabolism, and the breakdown of toxins. Important CYP2C genes, CYP2C8 and CYP2C9, have polymorphisms that affect a person's susceptibility to several metabolic diseases and some malignancies (Dawed et al, 2010; Shahabi et al, 2014). On chromosome 10q24 are the two genes. The metabolism of anti-diabetic medications, such as those in the thiazolidinedione family, which includes pioglitazone and rosiglitazone, may be influenced by the CYP2C8 gene (Niemi et al, 2003). One of the most prevalent CYP enzymes in the liver, the CYP2C9 gene catalyzes the breakdown of over 100 medicinal medications, such as thiazolidinediones and sulfonylureas, and makes up around 18% of the cytochrome P450 protein in liver microsomes (Holstein et al, 2005; Hu et al, 2018). The catalytic activity of CYP2C8 and CYP2C9 enzymes can be influenced by genetic variations, which can also impact the body's metabolism of xenobiotics. Conversely, arachidonic acid (AA) epoxygenases, which facilitate the synthesis of epoxyeicosatrienoic acids (EETs), are likewise identified as members of the CYP2C gene family (Dawed et al, 2016). Research on animals has largely and repeatedly demonstrated that EETs have a protective function in the onset and development of DM (Gangadhariah et al, 2017) EETs can raise insulin and plasma glucose levels as well as enhance glucose tolerance. Elevated EET levels are associated with reduced dyslipidemia and diminished immune responses. They can also trigger the PPAR-γ and MAPK pathways and boost the synthesis of atrial natriuretic peptide (Schafer et al, 2015; Luria et al, 2011). The aforementioned research link EET generation to a reduction in diabetes mellitus and its associated cardiovascular risks. Thus, variations in the CYP2C family of genes may have an impact on EET synthesis.

Tenth chromosome-based cytochrome CYP450 enzymes, including the *CYP2C8* gene, encode cytochrome CYP450 enzymes. It makes up roughly 7% of all the *CYP450* genes present in the liver of an individual. More than 60 therapeutic medications, including those for diabetes and cancer, are metabolized by it. There are several residues that have been found. The tertiary structure of the gene and the active regions in *CYP2C8* indicate that the gene is near the T or the Y form, The kidneys, brain, and intestine have all been found to have the CYP2C8 protein. Arachidonic acid in the kidney is known to be converted by the CYP2C8 protein into active receptors that influence water reabsorption and sodium transport. (Stage *et al*., (2013).

The aim of this research was to determine the genetic polymorphisms of the *CYP2C8* gene at the locus of variations rs1934953 C/A/G/T and rs1934952 C/T, as well as their association with the risk of type 2 diabetes in patients from Iraq.

Martial and methods

Ethical approval

The Institutional University of Diyala Affi liated Sixth People's Hospital assured ethical approval according to the Helsinki Declaration II. All subjects provided written informed consent to participate.

Participants

The research investigation was carried out at the University of Diyala in Iraq, in the Molecular Genetics Lab of the Faculty of Education for Pure Sciences. The current study concentrated on visitors to the Baaquba Teaching Hospital's consulting clinics who were in good health and those who had type 2 diabetes. Blood samples were taken between October 2022 and February 2023 from both healthy individuals and people with type 2 diabetes. A total of 48 study samples were used; 24 were from individuals without type II diabetes and 24 individuals with type II diabetes. Patients diagnosed with type 2 diabetes according to WHO criteria (fasting plasma glucose > 7.0 mmol/L and/or 2-h post challenge plasma glucose ≥ 11.1 mmol/L) were treated with insulin or oral hypoglycemic medications. The plasma glucose levels of the controls were either 6.1 mmol/L while fasting or 7.8 mmol/L two hours after the challenge, depending on the test, which was performed orally. People who have type 1 diabetes

Clinical measurement

DNA was extracted using the System DNA Miniprep Blood ReliaPr extraction kit, which was supplied by Bioneer in South Korea. To amplify the *CYP2C8* gene at the location of variants rs1934953 and rs1934952, mixture for the polymerase chain reaction 1.5 µl forward primer 5"-ACAAACAGTCATTTGTGACT-"3 , 1.5 microliters of

the reverse primer and 5"-GGACTCTGCATGCTTCTTGC-3" , 3 µl DNA, 5 µl master mix, and 14 µl free nuclease water. For every sample, the reaction product had a total volume of 25 microliters. The reaction mixture for the samples of healthy people and diabetes patients was then added to the polymerase chain reaction device. The following reaction conditions were programmed into the apparatus: five minutes at 94°C for initial denaturation, thirty seconds at 94°C for denaturation, thirty seconds at 63°C for primer annealing, five minutes at 72°C for extension, and five minutes at 72°C for final extension. This was carried out due to a total of 35 cycles involving primer annealing, denaturation, and extension. After the data from the polymerase chain reaction were collected, the samples were electrophoresed for 1.5 hours at 90 volts on a 1% agarose gel.We evaluated the insulinogenic index and used the trapezoidal rule to obtain the areas under the curves for glucose and insulin (GAUC and IAUC, respectively). Insulin sensitivity and secretory capacity were measured in individuals using the homeostasis model assessment (HOMA) (Matthews et al, 1985). Additionally, the Gutt index as well as the first and second phases of insulin secretion as well as the Stumvoll et al. indices were employed (Stumvoll et al, 2001; Gutt et al, 2000). The amplification product was shipped to Macrogen Company in South Korea, where it enabled Sanger nucleotide sequencing of the *CYP2C8* gene. The Hardy-Weinberg equation was used to ascertain which genotype was a causative factor and which genotype was a protective factor based on the analysis of the nucleotide sequencing data using the Genius application (Alzubadiy *et al*., 2019).

Statistical analysis

The chi-square test was utilized to evaluate the Hardy-Weinberg equilibrium and confirm the normal genotype distributions for each tag SNP. A P-value of less than 0.05 was deemed statistically significant. Linkage disequilibrium (LD) analysis was done paired using Haploview 4.2. The genotype distribution of cases and controls was analyzed using logistic regression. The relationship between SNP genotype and the occurrence of T2DM was examined using a genetic additive model; odds ratios (Ors) with standard errors or 95% confidence intervals (Cis) were displayed, and Ors were assigned based on minor allele.

The multiple hypothesis test correction (empirically P value) was achieved by using the permutation test under 10,000 permutations. Pointwise empirically P values were computed under 10,000 permutations while taking the local genome region's LD level into consideration. The association between the occurrence of a disease and a haplotype block was determined using haplotype analysis. Logistic regression was used to calculate genotype interactions. Through the use of additive modeling and linear regression, the impact of genotype on quantitative attributes was investigated. Prior to linear regression analysis, quantitative traits with a skewed distribution were logarithmically converted. SAS Institute, Cary, NC, USA) provided PLINK and SAS 9.3 software for all of these analyses. It was determined that a two-tailed P-value of less than 0.05 indicated statistical significance.

Results

***CYP2C8* gene amplification product for the coding sequence that contains both variants, rs1934953 and rs1934952, in type II diabetic patients and healthy controls.**

The results of *CYP2C8* gene amplification from mitochondrial DNA are displayed in Figure 1. for both type 2 diabetic patients and healthy persons. In each patient and healthy sample, should the amplification findings demonstrate that the variations rs1934953and rs1934952 have a molecular weight of 882 bp at the location of the resultant bands.

Comparison of the GenBank sample and the research samples for the nitrogenous bases alignment of the *CYP2C8* gene at the rs1934953 variant location.

The results in Figure 2 when comparing the nucleotide sequence of the *CYP2C8* gene between the GenBank sample and the samples of the current research showed the presence of a genetic mutation of the translocation type in samples of patients with type 2 diabetes at position 333 of the nucleotide sequence of the gene.

Comparison of the GenBank sample and the research samples for the nitrogenous bases alignment of the *CYP2C8* gene at the rs1934952 C/T variant location.

The results in Figure 3 when comparing the nucleotide sequence of the *CYP2C8* gene between the GenBank sample and the samples of the current research showed the presence of a genetic mutation of the translocation type in samples of patients with type 2 diabetes at position 363 of the nucleotide sequence of the gene.

Genotypes of the *CYP2C8* gene at the variant location rs1934953 in a group of type 2 diabetic patients and healthy controls.

In order to assess the association between *CYP2C8* genotypes and alleles at the rs1934953 variant site in a cohort of type 2 diabetics and healthy controls, Table 1's findings indicate that the gene has three genotypes: CC, CT, and TT. Based on Fisher's probability, the statistical analysis revealed no significant differences between the diabetes patient group and the healthy population, with Fisher's probability values reaching 0.701, 0.524, and 0.579, respectively. The p_value of CC (0.701), CT(0.546) and TT(0.579) show that there is bon significant relationship between patient group and healthy population.

According to the Hardy-Weinberg law, the distribution of genotypes and allelic frequencies of the *CYP2C8* gene for the rs1934953 variant site between the type 2 diabetic group and the healthy control group was compared. Table 2's results indicated that there were no significant differences between the observed and expected values for the type 2 diabetic group, with the Hardy probability being Hardy 0.2207, as for the healthy group, the results

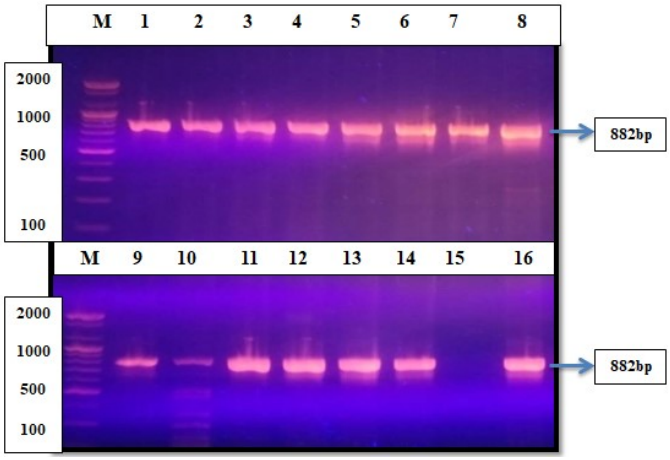

Figure 1. The amplification of a portion of the *CYP2C8* gene for the coding segment containing the variants rs1934953 and rs1934952 in type II diabetic patients from the Iraqi population. The samples were transferred to an agarose gel at a concentration of 1.5% for 1.5 hours at a voltage of 90 volts, stained with ethidium bromide dye, and exposed to ultraviolet light. Samples from 1 to 8 are patient samples, whereas samples from 9 to 16 are healthy samples.

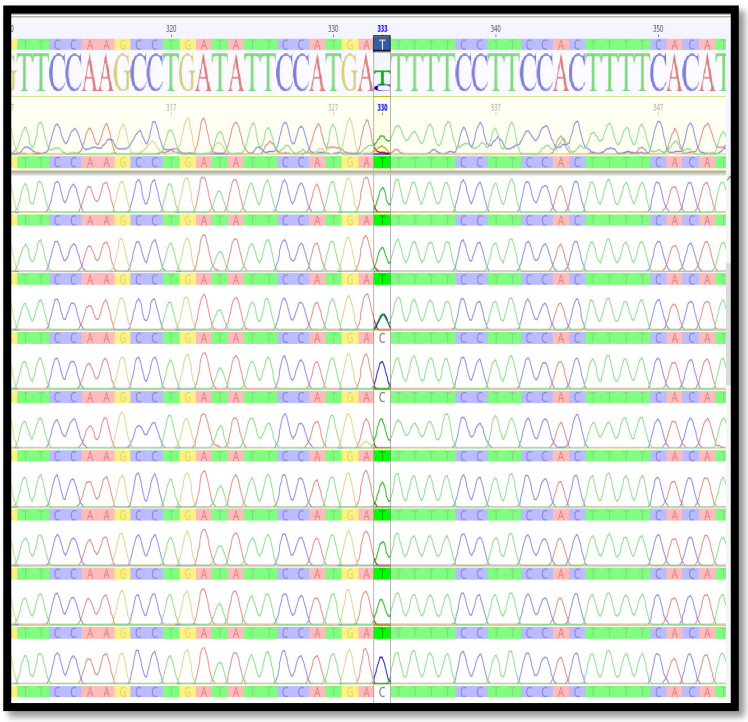

Figure 2. Compares the alignment of the nitrogenous bases of a segment of the *CYP2C8* gene between samples from type II diabetes patients, healthy controls, and the GenBank sample in order to show the position of the rs1934953 C/A/G/T variant and the kind of mutation (NCBI, 2023).

Table 1. Genotype distribution and allele frequency of *CYP2C8* rs1934953 C/A/G/T SNPs. NS: Not Significant, ** 0.001, * Significant P≤ 0.05

Genotype *CYP2C8* rs1934953 C/A/G/T	**Patients No.(%)**	**Control No.(%)**	**Fishers/P-value**	**O.R. (C.I)**
CC	4 (16.66%)	4 (16.66%)	0.701NS	1.00 (0.20 – 5.01)
CT	8 (33.33%)	6 (25%)	0.546NS	1.50 (0.41 – 5.53)
TT	12 (50%)	14 (58.33%)	0.579NS	0.857 (0.50 – 1.43)
Total	24 (100%)	24 (100%)		
Allele	*Frequency*			
C	16 (33.33%)	14 (29.17%)	O.R. (C.I.) = 1.21 (51 – 2.92)	
T	32 (66.67%)	34 (70.83%)	O.R. (C.I.) = 0.82 (0.34 – 1.98)	

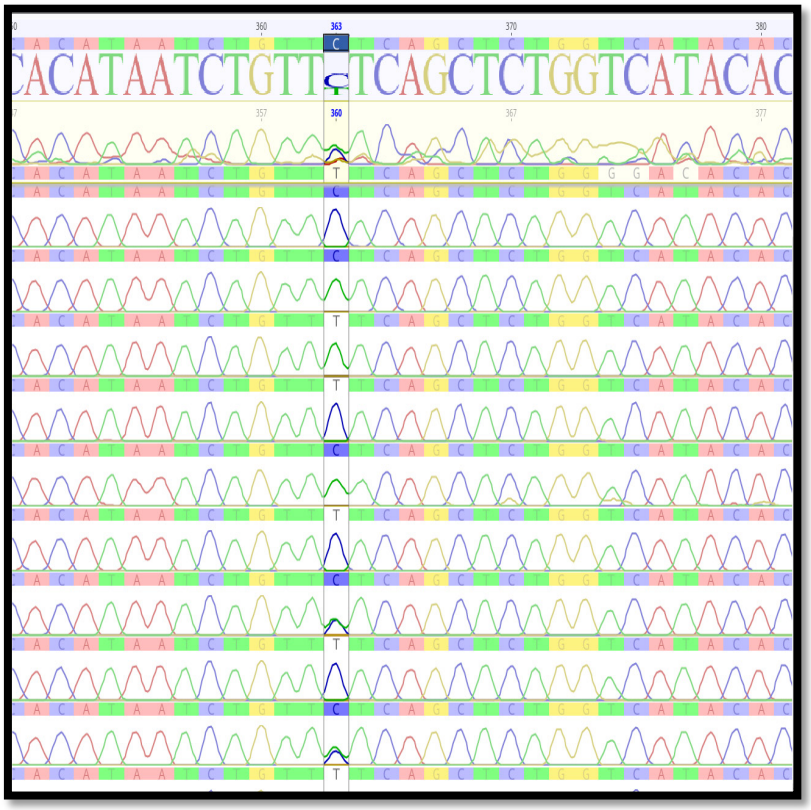

Figure 3. Compares the alignment of the nitrogenous bases of a segment of the *CYP2C8* gene between samples from type II diabetes patients, healthy controls, and the GenBank sample in order to show the position of the rs1934952 C/T variant and the kind of mutation (NCBI, 2023).

Table 2. Expected frequencies of genotype and alleles of the coding region *CYP2C8* rs1934953 C/A/G/T for by using Hardy-Weinberg equilibrium**.** NS: Not Significant, ** 0.001, * Significant P≤ 0.05

Genotypes and Alleles Groups		**CC**	**CT**	**TT**	**C**	**T**	**Hardy P-values**
Patients Genotypes	Observed no.	4 16.66%	8 33.33%	12 50%	16 33.33%	32 66.67%	0.2207 NS
	Expected no.	2.67 11.11%	10.67 44.44%	10.67 44.44%	Not diagnosed		
Control Genotypes	Observed no.	4 16.66%	6 25%	14 58.33%	14 29.17%	34 70.83%	0.053*
	Expected no.	2.04 8.51%	9.92 41.32	12.04 50.17	Not diagnosed		

Table 3. Genotype distribution and allele frequency of *CYP2C8* rs1934952 C/T SNPs. NS: Not Significant, ** 0.001, * Significant P≤ 0.05

Genotype *CYP2C8* rs1934952 C/T	**Patients No.(%)**	**Control No.(%)**	**Fishers/P-value**	**O.R. (C.I)**
CC	13 (54.16%)	14 (58.33%)	0.781NS	0.84 (0.26 – 2.71)
CT	6 (25%)	7 (29.16%)	0.759NS	0.81 (0.21 – 3.01)
TT	5 (20.83%)	3 (12.5%)	0.473NS	1.84 (0.37 – 10.36)
Total	24 (100%)	24 (100%)		
Allele	*Frequency*			
C	32 (66.67%)	35 (72.92%)	O.R. (C.I.) = 0.74 (0.30 – 1.80)	
T	16 (33.33%)	13 (27.08%)	O.R. (C.I.) = 1.35 (0.56 – 3.28)	

Table 4. Expected frequencies of genotype and alleles of the coding region *CYP2C8* rs1934952 C/T for by using Hardy-Weinberg equilibrium. NS: Not Significant, ** 0.001, * Significant P≤ 0.05

Genotypes and Alleles **Groups**		**CC**	**CT**	**TT**	**C**	**T**	**Hardy P-values**
Patients Genotypes	Observed no.	13 54.16%	6 25%	5 20.83%	32 66.67%	16 33.33%	0.032*
	Expected no.	10.67 44.44%	10.67 44.44%	2.67 11.11%	Not diagnosed		
Control Genotypes	Observed no.	14 58.33%	7 29.16%	3 12.5%	35 72.92%	13 27.08%	0.200 NS
	Expected no.	12.76 53.17%	9.48 39.5	1.76 7.34	Not diagnosed		

showed that there were considerable disparities between the observed and expected values, as the Hardy probability value reached 0.053.

Genotypes of the *CYP2C8* gene at the variant location rs1934952 in a group of type 2 diabetic patients and healthy controls.

In order to assess the association between *CYP2C8* genotypes and alleles at the rs1934953 variant site in a cohort of type 2 diabetics and healthy controls, Table 3's findings indicate that the gene has three genotypes: CC, CT, and TT. Based on Fisher's probability, the statistical analysis revealed no significant differences between the diabetes patient group and the healthy population, with Fisher's probability values reaching 0.781, 0.759, and 0.473, respectively.

According to the Hardy-Weinberg law, the distribution of genotypes and allelic frequencies of the *CYP2C8* gene for the rs1934952 variant site between the type 2 diabetic group and the healthy control group was compared. Table 4's results indicated that there were significant differences between the observed and expected values for the type 2 diabetic group, with the Hardy probability being Hardy 0.0321, as for the healthy group, the results showed that there were no significant differences between the observed and expected values, as the Hardy probability value reached 0.2001.

Discussion

In order to examine the genetic variation of the *CYP2C8* gene at the variant site rs1934953, this study was based on a comparison between two groups: samples from patients with type 2 diabetes were included in the first group, and samples from healthy individuals were included in the second. The results in Table 1 showed that the observed number of individuals harboring the homozygous CC genotype was 4 and the C allele was 16. In comparison to the healthy control group, which was recorded as 4, there was a tiny discernible rise observed in the type 2 diabetes patient group; based on the previously indicated percentages, they were 16.66 and 33.33, respectively. Fisher's probability P = 0.701 indicates that there are no significant differences between patients and healthy individuals. Therefore, the homozygous genotype CC and allele C are thought to be causative factors for the disease, as the odds ratios reached 1.00 and 2.21, respectively. The allele recorded 14 had a percentage of 29.17 and a percentage of 16.66. When compared to the control group, which reached 14 had a percentage of 58.33 and 34 had a percentage of 70.83, the homozygous genotype TT and allele T showed a substantial drop in the diabetes group, reaching 12 had a percentage of 50.0 and 32 had a percentage of 66.67, respectively. There are no significant differences between patients and healthy individuals, as indicated by Fisher's probability P = 0.579. Therefore, the T allele and the TT genotype are thought to be protective factors against the disease based on odds ratio values of 0.857 and 0.82, respectively. The study found that there were no significant differences between patients and healthy individuals. Therefore, the CT genotype and the C allele are considered causative factors for the disease, as indicated by odds ratio values of 1.50 and 1.21, respectively. The variant genotype and the C allele showed a significant increase in patients, reaching 8 with a percentage of 33.33 and 16 with a percentage of 33.33, respectively, compared to the control group, which reached 6 with a percentage of 25.0 and 14 with a percentage of 29.17, respectively. Based on the Hardy-Weinberg law, Table 2's results demonstrated that the three genotypes TT, CT, and CC and the allelic frequency of the *CYP2C8* gene at the rs1934953 C/A/G/T variant site were distributed in a genetically balanced manner in the group of type 2 diabetes patients. No statistically significant differences (P≤0.05) were found between the observed and expected values for any of the three genotypes or alleles, and the Hardy-Weinberg probability value was observed to be 0.053. The Hardy-Weinberg probability value for the healthy group was 0.053, indicating a genetic imbalance due to considerable disparities between observed and predicted values. In this regard, Polonikon *et al.* (2017) investigated the *CYP2C8* gene's genetic polymorphism at the rs1934953 variation site and demonstrated that the TC genotype is linked to an increased risk of coronary heart disease, as well as elevated triglyceride and low-density protein levels. Values indicated that the C allele is a causal factor for the disease the odd ratio was 1.08–1.28. According to the findings of Such *et al.* (2011), a study of the genetic polymorphism in the *CYP2C8* gene at the variant site rs1934951, the CC genotype is linked to an increased risk of osteoporosis and osteonecrosis, with odds ratios ranging from 1.44 to 2.60.

The authors mostly concentrated on pharmacogenomics in a prior investigation of the CYP2 gene family and diabetes. Genetic variations in CYP2C8 were observed to affect the efficacy of rosiglitazone and repaglinide, while changes in CYP2C9 were linked to blood sulfonylurea clearance (Hu et al, 2018). Data from our study indicated that genetic variations in CYP2C9 were also linked to the development of T2DM, and we identified a unique SNP in CYP2C9 that was linked to the development of T2DM.

The data displayed in Table 3 demonstrated that the observed number of patients harboring the homozygous CC genotype was 13 and the C allele was 32 at the location of the variant rs1934952 in the *CYP2C8* gene. Comparing the type 2 diabetes patient group to the healthy control group, a small decline was seen, with percentages of 54.66 and 66.67, respectively. The percentages for 14 and 35 were 58.33 and 72.92, respectively. P = 0.781 was determined as Fisher's probability since there are no significant differences between patients and the healthy control, since the odds ratio values for the homozygous CC genotype and the C allele reached 0.84 and 0.74, respectively, they are therefore regarded as protective factors against the disease. The homozygous genotype TT and the T allele

also exhibited a substantial rise in the diabetes group, reaching 5, with a percentage of 20.83, and 16, with a percentage of 33.33, respectively, compared to the control group, where the percentages reached 12.5 and 27.08. Fisher's probability, P = 0.473, indicates that there are no significant differences between patients and healthy individuals. Therefore, the T allele and the TT genotype are thought to be causal factors for the disease, as indicated by the odds ratio values of 1.35 and 1.84, respectively. While the control group reached 7, with a percentage of 29.16 and 35, with a percentage of 72.92, respectively, the variant genotype CT and the C allele showed a significant decrease in patients, reaching 6, with a percentage of 25.0 and 32, with a percentage of 66.67, respectively. Based on the fisher probability of P= 0.759, there are no significant differences between patients and healthy people, so it is considered Odds ratio values of 0.81 and 0.74 indicate that the CT genotype and the C allele are protective factors against the disease, respectively.

According to the Hardy-Weinberg law, the genotype distribution of the three genotypes TT, CT, and CC as well as the allelic frequency of the *CYP2C8* gene at the rs1934952 C/T variant site in the group of type 2 diabetes patients are not genetically balanced, as indicated by the results in Table 4. This is because there are statistically significant differences between the genotypes' observed and expected values. The healthy group was genetically balanced since there were large disparities between the observed and expected values, where the Hardy-Weinberg probability value approached 0.200. In contrast, the three genetic and alleles had a Hardy-Weinberg probability value of 0.0321. Accordingly, the researcher Gao *et al.*, (2022) examined the genetic polymorphism in the *CYP2C8* gene at the variation site rs1934952 and demonstrated that the T allele is a causative factor for the disease, as indicated by the value of Odds coefficient 1.2-1.8. The TT genotype is linked to the risk of developing immune system disorders, heart disease, and hypersensitivity.

Previous epidemiological data revealed a possible correlation between a higher risk of diabetes and low HDL values (Abbasi et al, 2013). According to our research, people with the A allele in rs1819173 had a greater level of HDL-C and a decreased chance of developing T2DM, which was in line with the previously cited epidemiological findings. It is hypothesized that rs1819173 could influence the risk of type 2 diabetes via modifying HDL-C levels.

Noteworthy are a few of the study's limitations. First, the genotype-disease analysis did not take into account lifestyle factors like alcohol and tobacco use. It is unknown if there were interactions between genetic variations and lifestyle variables. Secondly, every mutation examined in our research was found in non-coding areas, and further research should be done to determine whether EET levels and CYP2C enzyme activity are related. Second, every mutation examined in this study was found in a non-coding region; hence, future research should examine any possible connection between EET levels and CYP2C enzyme activity. Moreover, because of the mild impact of CYP2C8 and CYP2C9 variations, false positives shouldn't be discarded.

Conclusion

The analysis of the relationship between genetic variants in the CYP2C8 gene and the risk of type 2 diabetes in Iraqi patients concludes that there may be a connection that merits more research. The results offer important new understandings of the genetic components of type 2 diabetes susceptibility in this group; nevertheless, bigger sample numbers and more varied cohort studies are required to confirm these findings and clarify the underlying mechanisms.Iraqi patients with *CYP2C8* gene polymorphisms had a higher chance of acquiring type 2 diabetes since the TT genotype at the rs1934953 variation location is thought to be protective against the disease, whilst the CC and CT genotypes are thought to be causal factors. The CC and CT genotypes are thought to be protective factors against the condition, whereas the TT genotype is thought to be a factor that causes the disease at the variant location rs1934952. The results show there is non significant difference between patient group and healthy population.

Author contribution

S.A.Q.A., A.A.S. designed and conducted the experiment, analyzed data, prepared the initial draft, and finalized the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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