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The Role of SLC30A8 Rs13266634 Polymorphism with Type 2diabetes Mellitus-Related Hypertension in a Population of Wasit Province-Iraq

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Abstract: This case-control study was conducted from October 1, 2024, to January 30, 2025, and included 80 participants: 45 patients with type 2 diabetes mellitus (T2DM)-related hypertension (23 males, 22 females) and 35 healthy controls (18 males, 17 females). Genotyping of the *SLC30A8* rs13266634 polymorphism was performed using the TaqMan SNP Genotyping Assay, which revealed three genotypes: CC, CT, and TT. Among T2DM patients, genotype frequencies were CC: 26%, CT: 16%, and TT: 58%. In the control group, frequencies were CC: 34%, CT: 26%, and TT: 40%. Genotype and allele distributions conformed to Hardy–Weinberg equilibrium (χ^2 = 2.602, P = 0.272; χ^2 = 2.902, P = 0.088). The T allele was more prevalent in patients (66.28%) than in controls (52.86%), suggesting a possible risk association.Odds ratio analysis indicated that the TT genotype conferred an elevated, though non-significant, risk of T2DM (OR = 2.083, 95% CI: 0.840–5.165, P = 0.113). The CT and CC genotypes showed potential protective effects (OR = 0.561, P = 0.308; OR = 0.658, P = 0.403, respectively). In females, both TT and CC genotypes were associated with increased risk (OR = 2.851 and 1.578), while the CT genotype was protective (OR = 0.339, P = 0.11). Among males, the TT genotype showed a moderate risk (OR = 2.187), CC showed a strong association (OR = 17.903, P = 0.050), and CT was significantly protective (OR = 0.038, P = 0.003).Genetic model analysis revealed no statistically significant associations under dominant (CC+CT vs. TT, OR = 0.48, P = 0.113), recessive (TT+CT vs. CC, OR = 1.517, P = 0.40), or over-dominant (TT+CC vs. CT, OR = 1.780, P = 0.30) inheritance patterns. However, the TT genotype was consistently associated with increased disease risk trends.In conclusion, the SLC30A8 rs13266634 polymorphism—particularly the TT genotype—may serve as a potential genetic marker for increased susceptibility to T2DM-related hypertension, especially in specific subgroups such as males. Further studies with larger cohorts are warranted to validate these findings and explore their clinical utility in personalized risk assessment.

Keywords: SLC30A8, rs13266634, 2diabetes mellitus-related hypertension

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by insulin resistance and defective insulin secretion, contributing to a global health burden (Zimmet *et al*., 2014). One of the major comorbidities frequently observed in T2DM patients is hypertension, which significantly elevates the risk of cardiovascular complications and mortality (Cheng *et al.,* 2017). The coexistence of T2DM and hypertension worsens clinical outcomes, necessitating an in-depth understanding of the genetic and molecular factors that predispose individuals to this dual condition.

Genetic susceptibility plays a pivotal role in the development of both T2DM and hypertension. The *SLC30A8* gene, encoding the zinc transporter ZnT8, has been implicated in the regulation of insulin secretion by pancreatic beta cells (Sladek et al., 2007). The *rs13266634* single nucleotide polymorphism (C>T), which results in an amino acid change from arginine to tryptophan (Arg325Trp), has been consistently associated with altered risk of T2DM in various populations (Zhou *et al.*, 2014). This polymorphism is believed to affect zinc transport and insulin granule stability, potentially influencing glucose homeostasis and disease progression.

While several studies have explored the role of *SLC30A8 rs13266634* in T2DM susceptibility, its impact on hypertension development in T2DM patients remains under-investigated, especially within specific ethnic groups such as those in Wasit province. This regional focus is important due to potential genetic and environmental differences affecting disease risk.

The present study aims to investigate the association between the *SLC30A8 rs13266634* polymorphism and susceptibility to hypertension in T2DM patients from Wasit province. Understanding this association may provide valuable insights for risk assessment and personalized treatment strategies in T2DM-related hypertension.

2.Material and Methods

2.1. Study subjects

A total of 80 participants :45 confirmed patients with diabetes and

35 healthy individuals as controls were selected by using a convenient

sampling method.

1- Type 2 diabetes mellitus –related hypertension patients group: 45 patients with T2DM-related hypertension 22males and 23

females), and their age range was between 40–75 years (58.84 ± 8.20) years,

median= 59 years).

2- Control group: the control group which comprised of 35 healthy individuals (18

males and 17 females) and their age range between 40-75 years (54.77 ± 11.63)

years, median=50 years).

2.2.Genomic DNA Extraction From Blood

Genomic DNA was extracted from whole blood by using Quick-gDNA Blood MiniPrep Catalog Nos. D3072 and D3073 The kit contents of this technique list in table 2.4. The quality of pure, integral, and intact genomic DNA was estimated by Nanodrop by using an A260/A280 absorbance ratio between 1.8 to 2.0 indicate that high quality (Desjardins and Conklin,2010).

2.3. Prepare of custom SNPs genotyping solution for *SLC30A8 rs13266634* polymorphism (genotyping) using TaqMan assay

This study used TaqMan custom SNP genotyping assay from Thermo Fisher Scientific Company for detecting SNPs for *SLC30A8 rs13266634* . Also, it was applied the allele-specific discrimination technique by using real-time PCR (Real-time polymerase chain reaction). The reference (wild) and alternative (variant) alleles for *SLC30A8 rs13266634* were referred to as in NCBI. The amount of each individual component needed for the screening of SNPs was shown in table 2.6 and the temperature and timing settings used for the screening of SNPs in table Table 1

Table 1:Details of SNPs

Gene name	**Catalog No.**	**Polymorphism**	**Location**	**Assay ID**	Context Sequence (VIC/FAM)
solute carrier family 30 member 8 *SLC30A8*	**4351379 rs13266634**	**C/T, Transition substitution**	**Chr.8:117172544 on Build GRCh38**	**C____357888_10**	TGCTTCTTTATCAACAGCAGCCAGC**[C/T]**GGGACAGCCAAGTGGTTCGGAGAGA

3. Results

3.1. Genotype and Allele Distribution

The frequency of the **TT** genotype was markedly higher in diabetic patients (58%) compared to controls (40%), while the **CT** and **CC** genotypes were found less frequently in patients (16% and 26%, respectively) than in controls (26% and 34%, respectively). Regarding allele distribution, the **T** allele was predominant in diabetic patients (66.28%) relative to controls (52.86%), whereas the **C** allele was underrepresented among patients (33.72%) compared to controls (47.14%). These results imply a potential association between the **T** allele and increased risk of diabetes.

3.2. Genotypic Association of *SLC30A8 rs13266634* with Diabetes Risk

- **TT genotype**: *OR* = 2.083, *P* = 0.113 (not statistically significant)
- **CC genotype**: *OR* = 0.658, *P* = 0.403 (protective effect)
- **CT genotype**: *OR* = 0.561, *P* = 0.308 (a reduced risk of diabetes)

These findings suggest a possible role of the **T** allele as a risk factor, while the **C** allele may exert a protective effect against type 2 diabetes.

3.3. Gender-Stratified Genotypic Risk Analysis

In female participants, the **TT** genotype was associated with an increased, but non-significant, risk of diabetes (OR = 2.851; 95% CI: 0.777–10.467; *P* = 0.114). Similarly, the **CC** genotype showed a higher odds ratio of 1.578 (95% CI: 0.2539–9.817; *P* = 0.624). The **CT** genotype, however, was associated with a decreased risk (OR = 0.339; 95% CI: 0.0902–1.278; *P* = 0.11), although this too did not reach statistical significance.

Among male participants, the **TT** genotype showed a non-significant association with diabetes risk (OR = 2.187; 95% CI: 0.6129–7.808; *P* = 0.227). The **CT** genotype demonstrated a statistically significant protective effect, with an OR of 0.038 (95% CI: 0.0042–0.347; *P* = 0.003). Conversely, the **CC** genotype was associated with a markedly increased risk (OR = 17.903; 95% CI: 0.9453–339.076; *P* = 0.050), which was borderline significant. These gender-

specific results underscore potential sex-dependent differences in the genetic susceptibility to diabetes conferred by the *SLC30A8* variant.

3.4. Evaluation of Genetic Models for *SLC30A8 rs13266634*

To further evaluate the relationship between the *SLC30A8 rs13266634* polymorphism and diabetes, three genetic models were applied: dominant, recessive, and over-dominant.

Under the **dominant model** (CC + CT vs. TT), the OR was 0.48 (95% CI: 0.1936–1.19; P = 0.113), suggesting a non-significant protective effect of the C allele. The **recessive model** (TT + CT vs. CC) showed a non-significant increased risk of diabetes, with an OR of 1.517 (95% CI: 0.5708–4.035; P = 0.40). The **over-dominant model** (TT + CC vs. CT) also indicated a non-significant increased risk, with an OR of 1.780 (95% CI: 0.5872–5.397; P = 0.30). These data suggest that while trends are apparent, none of the genetic models achieved statistical significance in this population.

4. Discussion

This investigation evaluated the impact of the SLC30A8 rs13266634 polymorphism on susceptibility to type 2 diabetes mellitus (T2DM) and T2DM-related hypertension in a cohort from Wasit Province, Iraq. The genotype frequencies for rs13266634 adhered to Hardy-Weinberg equilibrium, consistent with several population-based genetic studies that have reported similar equilibrium, suggesting that allele distribution is stable and suitable for association analyses (Brown *et al*., 2020; Ngwa *et al*., 2023).

Gender-specific analysis revealed more nuanced associations: in males, the CT genotype showed a significant protective effect, and the CC genotype was borderline associated with increased diabetes risk. Females showed non-significant trends for risk with the TT genotype and protection with CT. These findings align with evidence that sex hormones and gender-specific epigenetic modifications can modulate gene expression and β-cell function, potentially influencing how genetic variants manifest in disease (Kautzky-Willer *et al*., 2016).

In previous studies that have investigated the association of polymorphisms of several factors and other biomarkers among patients with type2 DM from Wasit province, (Yousif and Ghali,2021), revealed that IL-10 is a major contributor to the onset of type 2 diabetes mellitus and there may be a correlation between low levels of interleukin-10 and type two diabetes(Al-Sarray and Ahmed ,2021) found that may be a correlation between high levels of TNF-α and type 2 diabetes mellitus.(Shamkhi and Ahmed ,2021), displayed that levels of SIRT1 may be not associated with type2 diabetes mellitus. Furthermore, the cell free mitochondrial DNA increases significantly in patients with type2 diabetes mellitus (Hussein and Ghali,2022). COX-1 is a major contributor to the onset of type 2 diabetes and there may be an association between low levels of cyclooxygenase-1and type 2 diabetes (Jebil and Ghali,2021). The association analysis of IL-17AG197A gene polymorphism with T2DM displayed that heterozygous AG genotype of IL17AG197A showed a risk association among T2DM with OR=1.24 CI95% (0.31 - 5.01) p-value =1.00 and the G allele was associated with an increased risk ofT2DM (Khidhum and Ahmed,2022). (Mahmood and Ghali,2022), revealed that there was an association between the polymorphism of Osteoprotegerin (OPG) polymorphism and susceptibility to type2 diabetes mellitus. (Mahmood and Ghali,2022b), found also that there may be a correlation between high

levels of OPG and T2DM. Ghulam and Ahmed ,2025 investigated the association between he glutathione peroxidase 4 (GPX4) geners713041 polymorphism and hypertension in an Iraqi cohort, with emphasis on sex-specific effects and genetic models.They found that GPX4 rs713041 T allele is a genetic risk factor for hypertension in the Iraqi population, particularly among males. GPX4 polymorphism genotyping may serve as a potential biomarker for early identification of individuals at elevated risk.

5. Conclusion

The SLC30A8 rs13266634 polymorphism—particularly the TT genotype—may serve as a potential genetic marker for increased susceptibility to T2DM-related hypertension, especially in specific subgroups such as males. Further studies with larger cohorts are warranted to validate these findings and explore their clinical utility in personalized risk assessment.

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