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Association of GSTP1 Ile105Val Polymorphism with Type 2 Diabetes in Sudanese Population.

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is associated with oxidative stress and genetic factors. Previous studies showed mixed results regarding glutathione S-transferase P1 (GSTP1) Ile105Val polymorphism and T2DM risk. This case-control study investigated the association between GSTP1 codon 105 (Ile to Val) polymorphism and T2DM susceptibility among Gezira State population, Sudan.

Objective: To investigate individual effect of GSTP1 Ile105Val polymorphism on predisposition to T2DM among Sudanese population.

Materials and methods: Eighty-six T2DM patients and ninety-six healthy controls participated. Genomic DNA was extracted and GSTP1 codon 105 polymorphism screened by PCR-RFLP method. Four genetic models (recessive, dominant, co-dominant, over-dominant) were used to evaluate genotype frequencies and associations.

Results:

Genotype distribution: T2DM patients: Ile/Ile 49.3% (34/69), Ile/Val 42.0% (29/69), Val/Val 8.7% (6/69). Controls: Ile/Ile 54.2% (52/96), Ile/Val 35.4% (34/96), Val/Val 10.4% (10/96) (P=0.676).

Allele frequencies: A allele 71% (T2DM) vs 72% (controls); G allele 29% vs 28%.

Genetic models: No significant associations (Recessive P=0.93, Dominant P=0.59, Co-dominant P=0.83, Over-dominant P=0.55).

Age association: Heterozygote AG genotype showed borderline older age (58.21 vs 52.90 years, P=0.05 over-dominant model).

Conclusion: GSTP1 Ile105Val polymorphism showed no significant association with T2DM risk in Sudanese population of Gezira State. Borderline age association with heterozygote genotype suggests possible age-dependent effect requiring further investigation

Keywords: GSTP1 polymorphism, type 2 diabetes mellitus, Sudan, PCR-RFLP, genetic association

Introduction

Type 2 diabetes mellitus (T2DM) poses a profound global public health burden, manifesting as a chronic, multifactorial, polygenic disorder (Bin Rakhis et al., 2022). Over the past five decades, its prevalence has shifted dramatically from high-income Western nations to the Western Pacific, Asia, and Africa, predominantly affecting low- and middle-income countries. In 2024, an estimated 589 million adults aged 20–79 years (one in nine) live with diabetes, accounting for 1.5 million direct deaths annually; projections forecast a rise to 853 million cases (one in eight) by 2050 (Abera et al., 2022; Galicia-Garcia et al., 2020; *IDF_Atlas_11th_Edition_2025_Global-Factsheet*, n.d.).

T2DM arises from oxidative stress induced by reactive metabolites interacting with physiological systems (Mahajan et al., 2018). Antioxidant enzymes, notably glutathione S-transferases (GSTs), provide critical protection. These phase II detoxification enzymes are categorized into cytosolic classes: mu (GSTM1), pi (GSTP1), theta (GSTT1), and alpha (GSTA1). Key polymorphisms include homozygous deletions giving GSTM1 and GSTT1 null genotypes, and the GSTP1 Ile105Val substitution (exon 5, codon 105), which impairs enzymatic activity (Singhal et al., 1994). It has been observed that functional polymorphisms of these enzymes contribute to pathophysiology of type 2 diabetes (Banerjee & Vats, 2014).

Evidence on the GSTP1 Ile105Val polymorphism's association with T2DM remains inconsistent: certain studies report heightened susceptibility in specific populations, whereas others detect no significant effect (Pavlovic et al., 2023; Liu et al., 2022). This discrepancy highlights a pressing research gap—the influence of GST polymorphisms on T2DM pathogenesis, particularly in understudied cohorts such as Sudanese populations, warrants further investigation.

Research question: Is there an association between GSTP1 codon 105 (Ile105Val) polymorphism and susceptibility to type 2 diabetes mellitus (T2DM) among Sudanese population?

The objective of this study was to investigate the Association of GSTP1 Ile105Val Polymorphism with Type 2 Diabetes in Sudanese Population.

Materials and Methods

Study Design and Subjects: A case-control study was conducted to investigate the role of GSTPI variant in the genetic predisposition to type 2 diabetes mellitus among population of Gezira state, Wad Madani City, Sudan. Eighty-six T2DM patients and ninety-six healthy controls participated in this case- control study. The cases group was selected from known T2DM patients who visited the Merits of December Revolution Health Centre for routine follow up and the healthy control group was selected from individuals who visited the National Cancer Institute for HLA investigations prior to kidney donation. T_2DM patients were 77.5% females with mean age 54.93 ± 10.99 years. Controls were 62.1% females with mean age 39.11 ± 11.57 years (P=0.000).

DNA Extraction and Genotyping

Genomic DNA was extracted using standard phenol-chloroform method. GSTP1 codon 105 polymorphism was screened by PCR-RFLP using primers:

Forward: 5'-GTAGTTTGCCCAAAGTCAAG-3'
Reverse: 5'-AGCCACCTGAGGGGTAAG-3'

PCR product (433 bp) was digested with Alw26I enzyme. Digestion patterns: Ile/Ile (328+105 bp), Ile/Val (328+222+106 bp), Val/Val (222+106 bp).

Statistical Analysis

Genotype frequencies tested for Hardy-Weinberg equilibrium. Associations evaluated using χ^2 test and Fisher's exact test across four genetic models. Odds ratios calculated by logistic regression. P<0.05 considered significant.

Results

Demographic and Laboratory Characteristics:

T2DM patients were significantly older (54.93±10.99 vs 39.11±11.57 years, P<0.001) with significantly higher FBS (193.02±76.09 vs 92.20±14.92 mg/dl, P<0.001), HbA1c (8.95±2.40 vs 5.87±0.55%, P<0.001), and triglycerides (136.92±67.60 vs 81.54±12.65 mg/dl, P<0.001). regarding BMI, no significant difference between T2DM patients and controls was detected (Table 1).

Table 1. Characteristics of the Study Groups

Characteristic	Patients (Mean ± SD)	Controls (Mean ± SD)	P-value
Age (years)	54.93±10.99	39.11±11.57	0.000*
BMI (kg/m²)	27.35±4.39	27.34±4.12	0.965
FBS (mg/dl)	193.02±76.09	92.20±14.92	0.000*
HbA1c (%)	8.95±2.40	5.87±0.55	0.000*
Triglycerides (mg/dl)	136.92±67.60	81.54±12.65	0.000*

*P<0.05 significant

GSTP1 Genotype Frequencies

T2DM (n=69): AA 49.3%, AG 42.0%, GG 8.7%

Controls (n=96): AA 54.2%, AG 35.4%, GG 10.4%

No significant differences across models (Table 2)

Association with T2DM Risk:

No significant associations between GSTP1 lle105val and T2DM across all models (Table 2).

Table 2. GSTP1 Genotypes and T2DM Across Genetic Models

Model	T2DM n(%)	Controls n(%)	OR (95% CI)	P-value
Recessive GG vs AA+AG				
AA+AG	63 (91.3)	86 (89.6)	0.94 (0.21-4.17)	0.93
GG	6 (8.7)	10 (10.4)		
Dominant AG+GG vs AA				
AA	34 (49.3)	52 (54.2)	1.25 (0.55-2.84)	0.59
AG+GG	35 (50.7)	44 (45.8)		
Co-dominant				
AA	34 (49.3)	52 (54.2)	1.00	0.83
AG	29 (42.0)	34 (35.4)	1.30	
GG	6 (8.7)	10 (10.4)	0.94	
Over-dominant AA+GG vs AG				
AA+GG	40 (58.0)	62 (64.6)	1.30 (0.55-3.04)	0.55
AG	29 (42.0)	34 (35.4)		

Association with Age: there was a borderline association between GSTP1 Genotypes and Age and age **(table 3**)

Table 3. GSTP1 Genotypes and Age Distribution

Model	Genotype	Mean Age	P-value
Co-dominant	AA	52.97	0.16
	AG	58.21	
	GG	52.50	
Dominant	AA	52.97	0.12
	AG+GG	57.23	
Over-dominant	AA+GG	52.90	0.05*
	AG	58.21	

*Significant at P=0.05

Discussion

Glutathione S-transferases (GSTs), a family of multigene and multifunctional detoxifying enzymes that protect cells from a range of toxic insults and oxidative stress, including GSTP1. Oxidative stress may cause cellular dysfunction and have a role in the pathogenesis of a number of human diseases, including diabetes mellitus, cancer, atherosclerosis, cardiovascular stroke, and bronchial asthma (Babusikova et al., 2009; Erciyas et al., 2004; Huang et al., 2004). GST polymorphisms can decrease enzyme activity and make them more susceptible to oxidative stress in β-cells (Wang et al., 2006).

This case-control study investigated the association between GSTP1 Ile105Val polymorphism and predisposition to type 2 diabetes mellitus (T2DM) susceptibility among Sudanese population in the middle region (Gezira state) by assuming recessive, dominant, co-dominant and over- dominant genetic inheritance models. We found no significant association between GSTP1 genetic variants and T2DM risk across all genetic models tested (table 2). These findings are consistent with the meta-analysis conducted by Liu et al. and other studies by Gönül et al. and Tang et al. which concluded that GSTP1 polymorphisms are not significantly connected with elevated T2DM risk (Gönül et al., 2012; Liu et al., 2022; Tang et al., 2013). Controversy, other studies like Stoian et al. and M. Banerjee et al. concluded that GSTP1 Ile105Val polymorphism was associated with increased risk of developing T2DM (Stoian et al., 2015) (Banerjee et al., 2019). These variations between previous research and our findings may be due to variations related to race, geography, and environment, or the susceptibility to T2DM might be related to the effect of other associated genetic polymorphism(s) in continuity of the gene locus.

. This result aligns with comprehensive meta-analytic evidence conducted by liu et al and a study by Saadat et al. which concluded that GSTP1 alone does not represent a strong independent risk factor for T2DM (Liu et al., 2022) . While polymorphisms in GSTM1, GSTT1, and GSTP1 have indicated possible links with T2DM risk, the GSTP1 Ile105Val (rs1695) variation did not approach statistical significance after corrections for false-positive (Liu et al., 2022; Saadat, 2017). Studies of GSTM1 and GSTT1 null genotypes by Nath et al. provide additional context, showing stronger associations with T2DM risk compared to GSTP1 variants alone (Nath et al., 2018). Furthermore, Azarova et al. demonstrated that combined GST polymorphisms contribute to T2DM susceptibility through sex-specific and gene-environment interactions (Azarova et al., 2018). These findings suggest GSTP1 polymorphism lacks significant independent impact on T2DM development, but though multi-gene interactions may play a role in specific genetic contexts.

In the current study, a significant correlation was found between age and the presence of the GSTP1 polymorphism. Although most models showed no significant age differences, the over-dominant model revealed heterozygote GA genotype carriers had higher mean age (58.2 years) compared to combined AA+GG genotypes (52.9 years), approaching statistical significance (p=0.05) (Table 3). This could be due to age-related variables including cumulative environmental exposures and increased oxidative stress with time, rather than a direct effect of aging on the genetic variant. It is also possible that unmeasured confounders or population-related factors play a role in this connection. As a result, this finding should be read carefully and in the light of the complex nature of T2DM and gene-environment interactions.

The lack of significant GSTP1-T2DM association in our Sudanese population highlights the polygenic nature of T2DM susceptibility

Conclusion

GSTP1 codon 105 (lle105Val) polymorphism showed no significant association with T2DM risk in Sudanese population of Gezira State. Heterozygote genotype GA was associated with older age which may indicate age-dependent effect.

Recommendations:

- To investigate combined GSTM1/GSTT1/GSTP1 genotypes in larger Sudanese cohorts to detect polygenic interactions missed by single-SNP analysis.
- Future studies should investigate combined GST haplotypes alongside gene-environment interactions in African populations
- To validate GA heterozygote age association (P=0.05) through longitudinal studies examining cumulative oxidative stress effects in Sudanese T2DM patients >50 years.
- To conduct community-based studies beyond hospital settings to reduce selection bias and improve generalizability to Sudanese population

References:

1. Abera, R. G., Demesse, E. S., & Boko, W. D. (2022). Evaluation of glycemic control and related factors among outpatients with type 2 diabetes at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A cross-sectional study. *BMC Endocrine Disorders*, *22*(1), 54. https://doi.org/10.1186/s12902-022-00974-z
2. Azarova, I., Bushueva, O., Konoplya, A., & Polonikov, A. (2018). Glutathione S-transferase genes and the risk of type 2 diabetes mellitus: Role of sexual dimorphism, gene–gene and gene–smoking interactions in disease susceptibility: **谷胱甘**肽 S-转移酶基因与 2 **型糖尿病**风险:**两性异形、基因-基因以及基因-吸烟相互作用**对疾病易感性的影响. *Journal of Diabetes*, *10*(5), 398–407. https://doi.org/10.1111/1753-0407.12623
3. Babusikova, E., Jesenak, M., Kirschnerova, R., Banovcin, P., & Dobrota, D. (2009). Association of oxidative stress and GST-T1 gene with childhood bronchial asthma. *Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society*, *60 Suppl 5*, 27–30.
4. Banerjee, M., & Vats, P. (2014). Reactive metabolites and antioxidant gene polymorphisms in Type 2 diabetes mellitus. *Redox Biology*, *2*, 170–177. https://doi.org/10.1016/j.redox.2013.12.001
5. Banerjee, M., Vats, P., Kushwah, A. S., & Srivastava, N. (2019). Interaction of antioxidant gene variants and susceptibility to type 2 diabetes mellitus. *British Journal of Biomedical Science*, *76*(4), 166–171. https://doi.org/10.1080/09674845.2019.1595869
6. Bin Rakhis, S. A., AlDuwayhis, N. M., Aleid, N., AlBarrak, A. N., & Aloraini, A. A. (2022). Glycemic Control for Type 2 Diabetes Mellitus Patients: A Systematic Review. *Cureus*. https://doi.org/10.7759/cureus.26180
7. Erciyas, F., Taneli, F., Arslan, B., & Uslu, Y. (2004). Glycemic control, oxidative stress, and lipid profile in children with type 1 diabetes mellitus. *Archives of Medical Research*, *35*(2), 134–140. https://doi.org/10.1016/j.arcmed.2003.10.002
8. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, *21*(17), 6275. https://doi.org/10.3390/ijms21176275
9. Gönül, N., Kadioglu, E., Kocabaş, N. A., Ozkaya, M., Karakaya, A. E., & Karahalil, B. (2012). The role of GSTM1, GSTT1, GSTP1, and OGG1 polymorphisms in type 2 diabetes mellitus risk: A case-control study in a Turkish population. *Gene*, *505*(1), 121–127. https://doi.org/10.1016/j.gene.2012.05.025
10. Huang, J., Tan, P. H., Tan, B. K. H., & Bay, B. H. (2004). GST-pi expression correlates with oxidative stress and apoptosis in breast cancer. *Oncology Reports*, *12*(4), 921–925.
11. *IDF_Atlas_11th_Edition_2025_Global-Factsheet*. (n.d.).
12. Liu, L.-S., Wang, D., Tang, R., Wang, Q., Zheng, L., Wei, J., Li, Y., & He, X.-F. (2022). Individual and combined effects of the GSTM1, GSTT1, and GSTP1 polymorphisms on type 2 diabetes mellitus risk: A systematic review and meta-analysis. *Frontiers in Genetics*, *13*, 959291. https://doi.org/10.3389/fgene.2022.959291
13. Mahajan, A., Wessel, J., Willems, S. M., Zhao, W., Robertson, N. R., Chu, A. Y., Gan, W., Kitajima, H., Taliun, D., Rayner, N. W., Guo, X., Lu, Y., Li, M., Jensen, R. A., Hu, Y., Huo, S., Lohman, K. K., Zhang, W., Cook, J. P., … McCarthy, M. I. (2018). Refining the accuracy of validated target identification through

coding variant fine-mapping in type 2 diabetes. *Nature Genetics*, *50*(4), 559–571. https://doi.org/10.1038/s41588-018-0084-1

14. Nath, S., Das, S., Bhowmik, A., Ghosh, S. K., & Choudhury, Y. (2018). The GSTM1 and GSTT1 Null Genotypes Increase the Risk for Type 2 Diabetes Mellitus and the Subsequent Development of Diabetic Complications: A Meta-analysis. *Current Diabetes Reviews*, *15*(1), 31–43. https://doi.org/10.2174/1573399814666171215120228
15. Pavlovic, D., Ristic, S., Djukanovic, L., Matic, M., Kovacevic, M., Pljesa-Ercegovac, M., Hadzi-Djokic, J., Savic-Radojevic, A., & Djukic, T. (2023). The GSTO2 (rs156697) Polymorphism Modifies Diabetic Nephropathy Risk. *Medicina (Kaunas, Lithuania)*, *59*(1), 164. https://doi.org/10.3390/medicina59010164
16. Saadat, M. (2017). Evaluation of glutathione S-transferase P1 (GSTP1) Ile105Val polymorphism and susceptibility to type 2 diabetes mellitus, a meta-analysis. *EXCLI Journal; 16:Doc1188; ISSN 1611-2156*. https://doi.org/10.17179/EXCLI2017-828
17. Singhal, S. S., Zimniak, P., Sharma, R., Srivastava, S. K., Awasthi, S., & Awasthi, Y. C. (1994). A novel glutathione S-transferase isozyme similar to GST 8-8 of rat and mGSTA4-4 (GST 5.7) of mouse is selectively expressed in human tissues. *Biochimica et Biophysica Acta (BBA) - Protein Structure and Molecular Enzymology*, *1204*(2), 279–286. https://doi.org/https://doi.org/10.1016/0167-4838(94)90019-1
18. Stoian, A., Bănescu, C., Bălaşa, R. I., Moţăţăianu, A., Stoian, M., Moldovan, V. G., Voidăzan, S., & Dobreanu, M. (2015). Influence of GSTM1, GSTT1, and GSTP1 Polymorphisms on Type 2 Diabetes Mellitus and Diabetic Sensorimotor Peripheral Neuropathy Risk. *Disease Markers*, *2015*, 638693. https://doi.org/10.1155/2015/638693
19. Tang, S.-T., Wang, C.-J., Tang, H.-Q., Zhang, Q., & Wang, Y. (2013). Evaluation of glutathione S-transferase genetic variants affecting type 2 diabetes susceptibility: A meta-analysis. *Gene*, *530*(2), 301–308. https://doi.org/10.1016/j.gene.2013.08.043
20. Wang, G., Zhang, L., & Li, Q. (2006). Genetic polymorphisms of GSTT1, GSTM1, and NQO1 genes and diabetes mellitus risk in Chinese population. *Biochemical and Biophysical Research Communications*, *341*(2), 310–313. https://doi.org/10.1016/j.bbrc.2005.12.195