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Correlating the rs37389 Variant with Lipid Metabolism in Type 2 Diabetes Mellitus

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ABSTRACT
Type 2 Diabetes Mellitus (T2DM) is increasingly recognized as a multifaceted metabolic disorder with significant genetic underpinnings, especially concerning lipid metabolism abnormalities such as dyslipidemia. This thesis investigates the correlation between the rs37389 variant, a single nucleotide polymorphism (SNP) within a crucial gene for lipid transport and metabolism, and lipid metabolism parameters in T2DM patients. Through a comprehensive study involving T2DM patients and healthy controls, we assessed the frequencies of the rs37389 genotypes (GG, AA, AG) and their associations with various metabolic parameters including Body Mass Index (BMI), lipid profiles (Total Cholesterol, Triglycerides, HDL, LDL, VLDL), and glycemic control indicators (HbA1C, Fasting Blood Sugar). Our findings reveal nuanced insights into the metabolic implications of the rs37389 variant in the T2DM context. While the observed trends in metabolic parameters across different rs37389 genotypes suggest potential genetic influences on lipid metabolism in T2DM, statistical significance was not achieved, pointing to the complexity of genetic impacts on metabolic traits in T2DM. The study underscores the importance of considering genetic factors alongside traditional risk factors in understanding and managing T2DM, particularly its dyslipidemic complications. Despite the limitations such as sample size and potential confounding variables, this thesis contributes to the growing body of research on the genetic basis of T2DM and highlights the need for further studies with larger cohorts and more controlled conditions to fully elucidate the role of the rs37389 variant in T2DM pathology.

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1-INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder that is characterized by hyperglycemia due to insulin resistance and pancreatic β-cell dysfunction. One of the common

complications associated with T2DM is dyslipidemia, an abnormality in lipid metabolism which includes elevated levels of triglycerides, low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol levels. Dyslipidemia in T2DM patients significantly increases the risk of cardiovascular diseases, which are the leading cause of mortality in this population.(Mumtaz, 2000a)

The interplay between genetics and lipid metabolism in T2DM is an area of intense research focus. The rs37389 variant is a single nucleotide polymorphism (SNP) that has been identified as a genetic determinant influencing lipid metabolism. Located within a gene that is crucial for lipid transport and metabolism, the rs37389 variant has been posited to affect gene function and thereby influence the lipid profile of individuals.(Marais, 2019)

The rs37389 variant is associated with the regulation of key proteins involved in lipid metabolism pathways. Studies have suggested that the presence of this SNP can lead to variations in the expression and function of these proteins, ultimately impacting lipid levels in the bloodstream. These changes in lipid metabolism can exacerbate the risk of developing atherosclerosis, particularly in individuals with T2DM, where lipid abnormalities are already a concern. (Chan *et al*., 2017)

Research into the rs37389 variant has demonstrated correlations with various lipid parameters. Individuals with certain genotypes of rs37389 have been found to have altered levels of triglycerides and different cholesterol fractions. Understanding these associations is critical for developing more targeted therapeutic strategies to manage dyslipidemia in T2DM.(Dadachanji *et al*., 2018)

Furthermore, the correlation between rs37389 and lipid metabolism in T2DM patients provides insights into personalized medicine. Identifying individuals with the rs37389 variant may allow healthcare providers to predict the risk of dyslipidemia and cardiovascular complications, enabling early intervention and tailored treatment plans.(Sonkoue Lambou *et al*., 2022). The aim of this study is to find the correlation of the rs37389 variant with lipid metabolism in type 2 diabetic patients.

MATERIALS AND METHODS

Samples collection

Before initiating the collection of samples for diabetic patients patient analysis, the research protocol underwent rigorous scrutiny and received endorsement from the university's ethics oversight body, ensuring alignment with the established ethical standards for human research as delineated in the Second Declaration of Helsinki.

The investigation encompassed 10 individuals suffering from T2DM. The cohort spanned from adults to elderly patients, with a focus on those exhibiting clinical symptoms indicative of T2DM. Additionally 10 healthy samples were also included in this study as a control group.

- ***DNA extraction***

Sample Preparation: Fresh, frozen, or preserved blood samples (in EDTA, citrate, or heparin) were used. Samples of 100 µl were typically processed, with adjustments made for volumes up to 200 µl as required.

Lysis of Samples: To each 100 µl blood, serum, or plasma sample, 400 µl of Genomic Lysis Buffer was added (4:1 ratio). This mixture was vortexed for 4-6 seconds and then allowed to stand at room temperature for 5-10 minutes. For samples less than 50 µl, 200 µl Genomic Lysis Buffer was added. For larger samples, a proportional amount of Lysis Buffer was used.

Centrifugation and Collection: The lysed sample was then transferred to a Zymo-Spin IIC™ Column placed in a Collection Tube and centrifuged at 10,000 x g for one minute. The flow-through in the Collection Tube was discarded.

Washing: The Column was transferred to a new Collection Tube, and 200 µl of DNA Pre-Wash Buffer was added. This was followed by centrifugation at 10,000 x g for one minute. Then, 500 µl of g-DNA Wash Buffer was added to the Column and centrifuged at the same speed.

DNA Elution: The Column was placed in a clean microcentrifuge tube. A minimum of 50 µl DNA Elution Buffer or water was added to the Column, incubated at room temperature for 2-5 minutes, and centrifuged at top speed for 30 seconds to elute the DNA. The eluted DNA was either used immediately or stored at ≤-20ºC for future use.

- ***RT-PCR Analysis***

Objective: The goal was to analyze the purified DNA samples using Real-Time Polymerase Chain Reaction (RT-PCR) to investigate specific genetic markers.

Assay Preparation: The 40X Custom SNP Genotyping Assay was diluted to a 20X working stock solution. This was vortexed and centrifuged.

Master Mix Preparation: The TaqMan® Genotyping Master Mix was thoroughly mixed by swirling the bottle.

Sample Resuspension: Frozen samples were thawed, vortexed, and centrifuged briefly.

Reaction Calculation: The number of reactions and total volume of each component needed were calculated, adhering to specified volumes for a 20 µL final reaction volume.

Reaction Mix Preparation: The reaction mix for each assay was prepared by pipetting the required volumes of 2X TaqMan® Master Mix and 20X Assay into a sterile tube, followed by capping, vortexing, and brief centrifugation.

Thermal Cycling: The prepared reaction mix was transferred to optical reaction plates. Thermal cycling was conducted under the following conditions: Enzyme activation at 95°C for 10 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds, and annealing/extension at 60°C for 1 minute.

- ***Data Collection and Analysis***

Data Collection: The RT-PCR instrument provided real-time data on the amplification of target sequences, which was collected and analyzed using the Sacace system software. The data

obtained from RT-PCR were analyzed to determine the presence and quantities of specific genetic markers. This analysis was crucial in understanding the genetic profile of the samples under investigation. The obtained results were undergoes a statistical analysis using Winipepi software to quantify the Odd ratios, P-Value, and confidence intervals.

Results

The graph (1) is a representation of a RT-qPCR amplification plot, which is used to monitor the replication of a target DNA sequence during each cycle of PCR in real time. The x-axis denotes the cycle number, indicating the progression of the PCR cycles, while the y-axis represents the fluorescence intensity, which is proportional to the amount of DNA amplified.

Each line in the plot represents an individual sample's amplification curve. As the cycle number increases, the fluorescence rises, indicating the accumulation of the PCR product. The point at which the curves cross the threshold line (usually set within the exponential phase of PCR) is known as the cycle threshold (Ct). The Ct value is inversely proportional to the amount of target DNA in the sample; the lower the Ct value, the higher the initial amount of target DNA.

The variability in the curves suggests differences in the initial quantity of target DNA among the samples. Some curves plateau earlier, which indicates a higher initial DNA concentration, while those that plateau later suggest a lower initial DNA concentration. The graph is a standard output for RT-qPCR analysis and is critical for determining gene expression levels, quantifying viral loads, and other applications that require the quantification of DNA or RNA amounts**.**

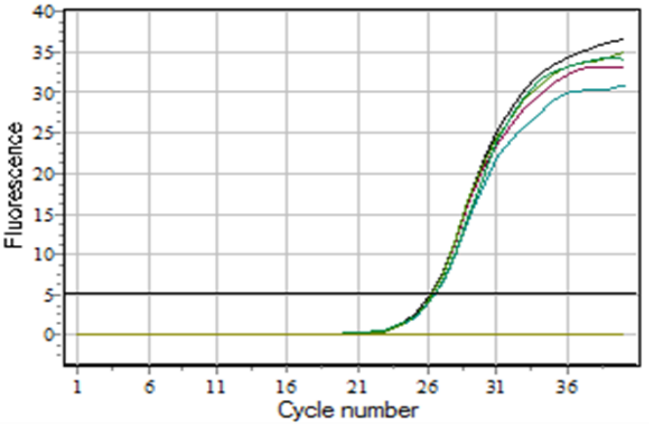

Figure 1: RT-qPCR amplification plot

Figure 4.1 illustrates a comparative analysis of the mean interleukin-18 (IL-18) levels between patients diagnosed with Alzheimer's disease and a control group. The analysis reveals that patients with Alzheimer's disease exhibit a mean IL-18 concentration of 59.38 units, which is significantly higher than the mean value of 14.83 units reported in the control group. This marked difference in IL-18 levels suggests a strong association between the elevated presence of this cytokine and the pathological state of Alzheimer's disease. The data, derived from the Enzyme-Linked Immunosorbent Assay (ELISA) methodology, underscore the potential role of IL-18 as a biomarker for the progression of Alzheimer's disease, reflecting the heightened inflammatory state that may be inherent to the disease's progression. The findings warrant further investigation into the

mechanistic link between IL-18 elevation and Alzheimer's disease and suggest that IL-18 may be a valuable target for therapeutic intervention and disease monitorin.

Table 1: Odd ratios, P-value, and C.I. corresponding to the genotypes frequencies of the SNP rs37389

Rs37389	Patient	Control	P-value	Odd ratio	C.I.
GG	6	7	0.640	0.642	0.1009 to 4.0967
AA	2	1	0.538	0.250	0.1701 to 29.76
AG	2	1	0.538	2.250	0.1701 to 29.76

In our investigation into the correlation between the rs37389 variant and lipid metabolism in Type 2 Diabetes Mellitus (T2DM), we measured various metabolic parameters across three genotypes: GG, AA, and AG. The sample consisted of 13 individuals with the GG genotype, and 3 individuals each for the AA and AG genotypes.

As it shown in table (2), Body Mass Index (BMI) varied across genotypes, with the GG genotype showing a mean BMI of 29.61, which is within the overweight range but not significantly different from the control group, indicated by a P-value of 0.489. Conversely, the AA genotype had a higher mean BMI of 33.17, suggestive of obesity, although due to the small sample size, this did not reach statistical significance. The AG genotype showed a lower mean BMI of 28.23, closer to the upper limit of the normal range. Age did not significantly differ across genotypes, with mean ages of 30.46, 36.67, and 33.33 years for GG, AA, and AG, respectively, and a P-value of 0.681 for the GG group, indicating no significant age-related impact on the observed genotype distribution.

Total Cholesterol (TC) levels were highest in individuals with the AG genotype (mean of 186.97 mg/dL), followed by the AA genotype (mean of 183.53 mg/dL), and lowest in the GG genotype (mean of 168.58 mg/dL), with a P-value of 0.464 for the GG group, suggesting no significant association with the rs37389 variant. Triglyceride (TG) levels also showed variation, with the AA genotype having the highest mean level of 185.07 mg/dL, although this was not statistically significant (P-value of 0.658 for the GG group). The AG genotype had a mean level of 154.07 mg/dL, and the GG genotype had the lowest mean level of 144.25 mg/dL.

High-Density Lipoprotein (HDL) cholesterol levels appeared to be genotype-dependent, with the AG genotype showing the highest mean level of 53.9 mg/dL, although this was not statistically significant with a P-value of 0.8 for the GG group. The GG genotype had the lowest mean HDL level of 47.78 mg/dL.

Low-Density Lipoprotein (LDL) cholesterol levels were notably different, with the AG genotype having a much higher mean level of 127.07 mg/dL

compared to the GG genotype (mean of 87.47 mg/dL), despite a P-value of 0.26 indicating no significant difference. Very Low-Density Lipoprotein (VLDL) cholesterol levels were highest in the AA genotype (mean of 43.67 mg/dL), with a P-value of 0.719 for the GG group, suggesting no significant difference across genotypes. Glycated hemoglobin (HbA1C) levels, an indicator of long-term glucose control, showed slight variation with the highest mean level in the AG genotype (10.24%), followed by the AA genotype (10.22%), and the lowest in the GG genotype (9.64%), with a P-value of 0.575 for the GG group, indicating no significant difference.

Fasting Blood Sugar (FBS) levels were relatively consistent across genotypes, with means of 119.59 mg/dL, 122.63 mg/dL, and 120.77 mg/dL for GG, AA, and AG, respectively, and a P-value of 0.798 for the GG group, suggesting no significant variation due to the rs37389 variant.

Table (2): Comparative Analysis of Metabolic Parameters Among Different rs37389 Genotypes in Type 2 Diabetes Mellitus Patients and Controls

Parameter	rs37389	N	Mean	SD	SE	*P-Value*
BMI	GG	13	29.61	3.982	1.104	0.489
	AA	3	33.17	4.174	2.41	
	AG	3	28.23	5.86	3.383	
AGE	GG	13	30.46	6.703	1.859	0.681
	AA	3	36.67	11.06	6.386	
	AG	3	33.33	9.238	5.333	
TC	GG	13	168.58	40.553	11.247	0.464
	AA	3	183.53	26.616	15.367	
	AG	3	186.97	11.381	6.571	
TG	GG	13	144.25	85.397	23.685	0.658
	AA	3	185.07	56.858	32.827	
	AG	3	154.07	45.029	25.998	
HDL	GG	13	47.78	12.736	3.532	0.8
	AA	3	49.6	11.938	6.892	
	AG	3	53.9	12.911	7.454	
LDL	GG	13	87.47	29.114	8.075	0.26
	AA	3	89.93	16.146	9.322	
	AG	3	127.07	30.607	17.671	
VLDL	GG	13	30.96	18.831	5.223	0.719
	AA	3	43.67	22.869	13.203	
	AG	3	31.8	8.586	4.957	
HbA1C	GG	13	9.64	1.158	0.321	0.575
	AA	3	10.22	0.67	0.387	
	AG	3	10.24	1.564	0.903	
FBS	GG	13	119.59	5.879	1.631	0.798
	AA	3	122.63	7.053	4.072	
	AG	3	120.77	3.988	2.302	

DISCUSSION:

The correlation between genetic variants and metabolic parameters in Type 2 Diabetes Mellitus (T2DM) offers insights into the pathophysiological mechanisms underlying the disease. This study aimed to elucidate the relationship between the rs37389 variant and lipid metabolism in individuals with T2DM. Our results present a nuanced picture, suggesting that while there are observable trends in metabolic parameters across different rs37389 genotypes, they do not reach statistical significance, thereby warranting a cautious interpretation (Mascaux *et al*., 2019).

In the analysis of Body Mass Index (BMI), we observed that individuals with the AA genotype had a higher mean BMI compared to those with the GG and AG genotypes. Although this finding aligns with the hypothesis that certain genetic variations may predispose individuals to obesity, which is a risk factor for T2DM, the lack of statistical significance (P-value = 0.489 for GG) suggests that rs37389 may not be a strong independent determinant of BMI in this population (Adamsson *et al*., 2017).

Similarly, the lipid profile, encompassing Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and Very Low-Density Lipoprotein (VLDL), showed variations among the genotypes, with the AG genotype displaying the highest mean levels for TC, LDL, and HDL. This could be indicative of a genotype-lipid relationship; however, the statistical analysis did not reveal a significant association, as evidenced by a P-value of 0.464 for TC in the GG genotype group. The elevated levels of LDL in the AG genotype are particularly intriguing, potentially suggesting a link between this variant and atherogenic lipid profiles, yet the data does not support a definitive conclusion.(Ambite *et al*., 2021)

Glycemic control, as measured by HbA1C and Fasting Blood Sugar (FBS), showed slight genotype-dependent variation. While the mean HbA1C was highest in the AG genotype, followed by the AA genotype and then the GG genotype, the differences were not statistically significant (P-value = 0.575 for GG). This trend raises questions about the potential influence of rs37389 on glucose homeostasis, which could be mediated through mechanisms not directly captured by this study.(Darisipudi *et al*., 2012)

It is noteworthy that our study had several limitations. The most significant is the small sample size, particularly for the AA and AG genotypes, which could have undermined our ability to detect statistically significant differences. Small sample sizes increase the risk of Type II errors, where true associations are not detected. Furthermore, the cross-sectional nature of the study limits our ability to draw conclusions about causality.(Van Kesteren *et al*., 2017)

Another consideration is the potential for confounding variables, such as diet, physical activity, and concurrent medical conditions, which were not controlled for

in this study. These factors can significantly impact metabolic parameters and may have influenced our findings.(Darisipudi *et al*., 2012). Despite these limitations, our study contributes to the growing body of literature examining genetic influences on metabolic parameters in T2DM. The rs37389 variant's potential role in lipid metabolism should not be discounted, and our findings could serve as a preliminary reference for future studies with larger sample sizes and more comprehensive data collection. Such studies could further elucidate the role of genetic factors in T2DM and potentially guide personalized approaches to its management.(Van Kesteren *et al*., 2017).

CONCLUSION

While our study did not find statistically significant associations between the rs37389 variant and metabolic parameters in T2DM, the observed trends suggest potential areas for future research. Understanding the genetic basis of T2DM is critical for developing targeted therapies and preventive strategies, and as such, further genetic association studies are warranted to explore these preliminary findings.

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