Article

Genetic Variants of the \( \text{PLCXD3} \) Gene Are Associated with Risk of Metabolic Syndrome in the Emirati Population

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Abstract: Phosphatidylinositol-specific phospholipase C X domain 3 (\( \text{PLCXD3} \)) has been shown to influence pancreatic \( \beta \)-cell function by disrupting insulin signaling. Herein, we investigated two genetic variants in the \( \text{PLCXD3} \) gene in relation to type 2 diabetes (T2D) or metabolic syndrome (MetS) in the Emirati population. In total, 556 adult Emirati individuals (306 T2D and 256 controls) were genotyped for two \( \text{PLCXD3} \) variants (rs319013 and rs9292806) using TaqMan genotyping assays. The frequency distribution of minor homozygous CC genotype of rs9292806 and GG genotype of rs319013 were significantly higher in subjects with MetS compared to Non-MetS (\( p < 0.01 \)). The minor homozygous rs9292806-CC and rs319013-GG genotypes were significantly associated with increased risk of MetS (adj. OR 2.92; 95% CI 1.61–5.3; \( p < 0.001 \)) (adj. OR 2.62; 95% CI 1.42–4.83; \( p = 0.002 \)), respectively. However, no associations were detected with T2D. In healthy participants, the homozygous minor genotypes of both rs9292806 and rs319013 were significantly higher fasting glucose (adj. \( p < 0.005 \)), HbA1c (adj. \( p < 0.005 \)) and lower HDL-cholesterol (adj. \( p < 0.05 \)) levels. Data from T2D Knowledge Portal database disclosed a nominal association of rs319013 and rs9292806 with T2D and components of MetS. Bioinformatics prediction analysis showed a deleterious effect of rs9292806 on the regulatory regions of \( \text{PLCXD3} \). In conclusion, this study identifies rs319013 and rs9292806 as additional risk factors for MetS in the Emirati population.

Keywords: phosphatidylinositol-specific phospholipase C X domain; HbA1c; type 2 diabetes; MetS; metabolic syndrome; MAF; minor allele frequency; BMI; body mass index; LDL; triglycerides; CJD; single-nucleotide polymorphism; SBP; diastolic blood pressure

1. Introduction

Metabolic syndrome (MetS) is a major health problem, referring to cluster risk factors that include obesity, dyslipidemia, hyperglycemia and hypertension [1–3]. Components of MetS, individually or
collectively, increase the risk of type 2 diabetes mellitus (T2D) and cardiovascular (CVD) diseases [4–6]. The International Diabetes Federation (IDF) estimates that a quarter of the adult population worldwide suffers from MetS [1]. The national estimates of MetS among adults in the United Arab Emirates (UAE) have reached to 40 percent [7], with nearly 75 percent of the population either overweight or obese [8]. Aside from lifestyle factors and physical inactivity, genetics is considered as an essential risk factor for metabolic syndrome [9].

Recently, we showed that the expression of PLCD3, a member of the PI-PLC family, is downregulated in human diabetic islets, inversely correlated with HbA1c and positively correlated with insulin secretion [10,11]. Further investigations revealed that PLCD3 is involved in insulin signaling and glucose sensing, suggesting that PLCD3 might be regarded as a candidate gene for pre-diabetes and metabolic syndrome. Despite the role of PLCD3 in β-cell function, until now no studies have linked genetic variants in the PLCD3 gene with T2D, MetS or its related traits.

Thus, the present study aims to investigate the association of two intronic SNPs “rs319013 and rs9292806” with T2D or MetS in the Emirati population.

2. Materials

2.1. Study Population

In total, 556 unrelated adult Emirati participants (306 T2D (120 males and 186 females)) and 256 controls (119 males and 137 females) were selected from two different cohorts were included for this study. The first cohort consisted of participants from UAE national diabetes and lifestyle study (UAEDIAB) that includes participants living in Dubai, Sharjah, and the Northern Emirates collected from door to door visits as described previously [12–14]. The second cohort includes participants from the All-New Diabetes in Sharjah and Ajman (ANDISA) study were patients recruited to this study based on their routine visit to the endocrinology clinic at the university hospital of Sharjah. The initial study was approved by the UAE ministry of health (MOHAP/DBX/SUBC/No.14/2017) and University of Sharjah ethics committee. A written informed consent with an extensive interview and a standard questionnaire were obtained from all the participants. Using the International Diabetes Federation (IDF) criteria for metabolic syndrome [3], the studied participants were re-classified into MetS and Non-MetS. The features for MetS include a waist circumference ≥102 cm for men and ≥88 cm for women, blood pressure ≥130/85, fasting plasma glucose levels ≥5.6 mmol/L, HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women and triglycerides ≥1.7 mmol/L. The MetS is defined as central obesity plus other two factors. For participants without waist circumference data, BMI ≥30 kg/m² were assumed as central obesity. Subjects who did not match the employed criteria for MetS selection were considered as Non-MetS.

All participants were requested to provide information on demographics, medical and family history of diabetes and current medications. Anthropometric parameters, including height, weight, mean systolic blood pressure, and diastolic blood pressure (average of three readings) were obtained from all the participants. Body mass index (BMI) values were computed by dividing weight in kilograms by height in meter square. Fasting blood samples were collected from participating individuals for a glucose test, HbA1c, and lipid profile. The same blood samples were used later for DNA extraction.

2.2. Genotyping Analysis

The genomic DNA was extracted from whole blood using pure link genomic DNA mini Kit (Invitrogen, Carlsbad, CA, USA). DNA concentration and purity were checked by Nano-drop 2000 C spectrophotometer (Thermo Scientific, Wilmington, NC, USA). Two tagging SNPs (Intronic variants) in PLCD3 gene rs319013 and rs9292806 have been selected for genotyping. Both rs319013 and rs9292806 were in very high linkage disequilibrium, for example, in the north European population [15] $\chi^2 = 0.977$ and $D' = 1.0$ (Figures 1 and 2). Data from 1000 Genomes Phase 3 showed that the combined population minor allele frequency of rs319013
is 0.43 and 0.44 for rs9292806. The distance between the SNPs is about 34-kilo base pairs (kbp) (https://jan2020.archive.ensembl.org/Homo_sapiens/Location/LD?db=core;focus=variation;pop1=373514;r=5:41382400-41416900;v=rs319013;vdb=variation;vf=49567201). The genotyping was performed by allelic discrimination real-time PCR using TaqMan assays for genotyping (Applied Biosystems, Foster City, CA, USA). The assay IDs are C_805815_10 for rs319013 and C_30418796_20 for rs9292806. All qPCR amplifications were carried out in a final reaction volume of 10 µL containing 1X firepol universal probe master mix (Solis Biodyne, Tartu, Estonia), 1X TaqMan genotyping assays, and 50 ng of template DNA. All amplifications and detections were conducted on genomic DNA in 96-well PCR plates using a QuantStudio three Real-time PCR (Applied Biosystems, Foster City, CA, USA). A minimum of two non-template control was included in each run. Thermal cycling was initiated with pre-PCR read followed by a denaturation step of 10 min at 95 °C followed by 50 cycles of 15 s at 95 °C, 60 s at 60 °C. Allelic discrimination analysis was performed using QuantStudio Real-Time PCR Software autocaller (Thermo Fisher, Waltham, MA, USA).

![Figure 1. Linkage disequilibrium rs319013 and rs9292806 (D’ = 1.0).](image1)

![Figure 2. Linkage disequilibrium rs319013 and rs9292806 (r² = 0.977).](image2)

2.3. Statistical Analyses

All the statistical analyses were carried out with SPSS version 26 (IBM, Armonk, NY, USA). The Hardy–Weinberg equilibrium was tested using a Chi-square test. Linkage disequilibrium was calculated using haploview. Haplotype frequencies were estimated by an Expectation–Maximization algorithm (EM algorithm) with haploview software [16]. The most common haplotype was used as the reference. The non-Gaussian variables are presented as median with interquartile range. An independent sample t-test was used to compare the difference between the groups, while the
Mann–Whitney U test was used for comparison of nonparametric variables. The genotype frequency differences between the categorized group (control vs. T2D or Non-MetS vs. MetS) were tested using a chi-square test. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by multinomial logistic regression with age and gender as covariates. The major allele was employed as the reference genotype. Analysis of variance (ANOVA) was used to compare different genotypic groups with anthropometric and biochemical parameters followed by application of Bonferroni post hoc test, while univariate general linear model (GLM) was used for adjusting covariates such as age and gender. The significance was set at \( p \)-value < 0.05. All the continuous normal variables are presented as mean ± standard deviation (SD).

3. Results

The anthropometric and clinical variables of the studied participants for control vs. T2D groups were shown in Table 1 and Non-MetS vs. Mets are presented in Table 2. Measurements of BMI, waist circumference SBP, HbA1c, fasting glucose and triglycerides were significantly higher in T2D and MetS groups when compared to controls (\( p < 0.001 \)), while levels of lipids profile (total cholesterol, LDL- and HDL-cholesterol) were, in general, lower.

### Table 1. Anthropometric and clinical characteristics of the studied groups.

| Parameters            | Control (n = 256) | T2DM (n = 306) | \( p \) Value |
|-----------------------|-------------------|----------------|---------------|
| N (M/F)               | 119/137           | 120/186        | <0.0001       |
| Age (Years)           | 43.3 ± 12.7       | 54.4 ± 10.8    | <0.0001       |
| BMI (kg/m\(^2\))      | 28.8 ± 5.2        | 31.2 ± 5.8     | 0.001         |
| Waist circumference   | 96.4 ± 12.9       | 103.5± 12.6    | 0.001         |
| SBP (mmHg)            | 125.3 ± 17.9      | 132.1 ± 16.2   | <0.0001       |
| DBP (mmHg)            | 77.6 ± 10.7       | 77.7 ± 10.3    | 0.89          |
| Glucose (mmol/L)      | 5.35 ± 0.66       | 10.0 ± 3.48    | <0.0001       |
| HbA1c (%)             | 5.44 ± 0.48       | 8.47 ± 1.51    | <0.0001       |
| Total Cholesterol (mmol/L) | 5.0 ± 0.94 | 4.6 ± 1.36    | <0.0001       |
| HDL-Cholesterol (mmol/L) | 1.39 ± 0.45 | 1.24 ± 0.36   | <0.0001       |
| LDL-Cholesterol (mmol/L) | 3.20 ± 0.82 | 2.78 ± 1.06   | <0.0001       |
| Triglycerides (mmol/L) | 1.1 (0.81–1.57) | 1.36 (1.05–1.92) | <0.0001 |

Data were presented as mean ± standard deviation for normal continuous variables; \( \# \) denotes continuous variables with non-Gaussian distribution and presented as median (1st–3rd quartile). Independent sample \( t \)-test and a Mann–Whitney U test were used to test differences between control and T2DM groups. Note: Waist circumference data available for 150 participants.

### Table 2. Anthropometric and clinical characteristics of the studied groups.

| Parameters            | Non-MetS (n = 341) | MetS (n = 215) | \( p \) Value |
|-----------------------|---------------------|----------------|---------------|
| N (M/F)               | 161/180             | 74/141         | <0.0001       |
| Age (Years)           | 46.5 ± 13.7         | 53.8 ± 10.1    | <0.0001       |
| BMI (kg/m\(^2\))      | 26.9 ± 4.0          | 34.9 ± 4.3     | <0.0001       |
| Waist circumference   | 93.5 ± 11.9         | 109.2 ± 8.8    | <0.0001       |
| SBP (mmHg)            | 125.2 ± 16.6        | 132.7 ± 16.7   | <0.0001       |
| DBP (mmHg)            | 76.3 ± 10.7         | 80.0 ± 9.6     | <0.0001       |
| Glucose (mmol/L)      | 7.0 ± 3.02          | 8.1 ± 3.55     | <0.0001       |
| HbA1c                 | 6.62 ± 1.82         | 7.79 ± 1.79    | <0.0001       |
| Total Cholesterol (mmol/L) | 4.84 ± 1.22 | 4.67 ± 1.17   | 0.15          |
| HDL-Cholesterol (mmol/L) | 1.37 ± 0.44 | 1.22 ± 0.34   | <0.0001       |
| LDL-Cholesterol (mmol/L) | 3.01± 1.02 | 2.90 ± 0.93   | 0.08          |
| Triglycerides (mmol/L) | 1.12 (0.84–1.68) | 1.41 (1.06–2.14) | 0.001 |

Data were presented as mean ± standard deviation for normal continuous variables; \( \# \) denotes continuous variables with non-Gaussian distribution and presented as median (1st–3rd quartile). Independent sample \( t \)-test and a Mann–Whitney U test were used to test differences between control and T2DM groups. Note: Waist circumference data available for 150 participants.
The genotype frequency distribution of both rs319013 and rs9292806 in the control and Non-MetS group were consistent with the Hardy–Weinberg equilibrium ($p > 0.05$). The genotype frequency distribution of both rs319013 and rs9292806 between T2D and control study groups are described in Table 3. No significant difference in genotype frequencies was found between control and T2D group. However, the genotype frequencies of rs319013 and rs9292806 were significantly different between MetS and Non-MetS subjects (Table 3, $p < 0.05$). The frequency of homozygous CC genotype of rs9292806 was significantly higher in individuals with MetS than Non-MetS (MetS 18% vs. Non-MetS 8%) (Table 3). Similarly, the frequency of homozygous GG genotype of rs319013 was significantly higher in individuals with MetS than Non-MetS (Mets 16% vs. controls 8.1%). The association of the PLCXD3 gene variants towards a predisposition to T2D or MetS was analyzed by multiple logistic regression considering age and gender as potential covariates. Our results indicated that both of the studied SNPs were not associated with risk of T2D (Table 4). However, the homozygous CC genotype of rs9292806 and homozygous GG genotype of rs319013 were significantly associated with risk of MetS (adj. OR 2.92; 95% CI 1.61–5.30; $p < 0.001$) (adj. OR 2.62; 95% CI 1.42–4.83; $p = 0.002$), respectively (Table 4). Furthermore, we investigated the association of the two SNPs rs319013 and rs9292806 with anthropometric parameters in control subjects. As shown in Table 5, the homozygous genotypes of both rs319013 (GG) and rs9292806 (CC) showed statistically significant higher levels of fasting glucose levels (adj. $p < 0.05$), HbA1c (adj. $p < 0.01$) and lower HDL-cholesterol (adj. $p <0.01$) levels (Table 5). Linkage disequilibrium analysis of our studied population indicated both rs319013 and rs9292806 were in very high linkage disequilibrium ($r^2 = 0.972$) (Figure 3). The frequency distribution of rs319013_G and rs9292806_C (i.e., GC) haplotype is more common MetS group compared to Non-MetS group, thus GC haplotype is associated with increased risk of MetS (OR 1.46; 95% CI 1.01–2.14; $p = 0.047$) (Table 6). However, no such differences were found in control vs. T2DM group (Table 6).

Figure 3. Linkage disequilibrium ($r^2 = 0.972$) analysis between rs319013 and rs9292806 in the Emirati population, $r^2$ indicates the squared correlation coefficient between two SNPs.
Table 3. Genotype frequency distribution of PLCD3 SNPs in Control vs. T2DM and Non-MetS vs. MetS subjects.

| Genotype | Control N (%) | T2DM N (%) | Chi² p Value | Non-MetS N (%) | MetS N (%) | Chi² p Value |
|----------|---------------|------------|--------------|----------------|-------------|--------------|
| rs9292806 |               |            |              |                |             |              |
| GG       | 125 (49.0)    | 169 (56.1) | 0.21         | 188 (55.5)     | 104 (49.3)  | 0.002        |
| CG       | 99 (38.8)     | 97 (32.2)  |              | 124 (36.6)     | 69 (32.7)   |              |
| CC       | 31 (12.2)     | 35 (11.6)  |              | 27 (8)         | 38 (18.0)   |              |
| rs319013  |               |            |              |                |             |              |
| TT       | 124 (49.2)    | 171 (57.0) | 0.18         | 187 (56.0)     | 106 (50.0)  | 0.015        |
| GT       | 97 (38.5)     | 98 (32.7)  |              | 120 (35.9)     | 72 (34.0)   |              |
| GG       | 31 (12.3)     | 31 (10.3)  |              | 27 (8.1)       | 34 (16.0)   |              |

Genotype frequency differences between Control vs. T2DM and Non-MetS vs. MetS groups were tested using Chi-square test.

Table 4. Odds ratios of genotypes the PLCD3 SNPs in control vs. T2DM and Non-MetS vs. MetS groups.

| Genotype | T2D OR (95 % CI) | p Value | T2D Adj OR (95 % CI) | Adj p Value | MetS OR (95 % CI) | p Value | MetS Adj OR (95 % CI) | Adj p Value |
|----------|------------------|---------|----------------------|-------------|-------------------|---------|-----------------------|-------------|
| rs9292806 |                  |         |                      |             |                   |         |                       |             |
| GG       | 0.72 (0.50–1.10) | 0.08    | 0.67 (0.43–1.03)     | 0.07        | 1.01 (0.69–1.47)  | 0.97    | 1.03 (0.69–1.55)       | 0.85        |
| CG       | 0.83 (0.49–1.42) | 0.51    | 0.80 (0.42–1.49)     | 0.47        | 2.54 (1.47–4.40)  | 0.001   | 2.92 (1.61–5.30)       | <0.001      |
| rs319013  |                  |         |                      |             |                   |         |                       |             |
| TT       | 0.73 (0.51–1.05) | 0.10    | 0.66 (0.36–1.02)     | 0.07        | 1.06 (0.72–1.54)  | 0.77    | 1.08 (0.72–1.63)       | 0.67        |
| GT       | 0.72 (0.42–1.25) | 0.25    | 0.69 (0.36–1.33)     | 0.28        | 2.22 (1.27–3.88)  | 0.005   | 2.62 (1.42–4.83)       | 0.002       |
| GG       |                  |         |                      |             |                   |         |                       |             |

Odds ratios (ORs) and 95 % confidence intervals for genotypes were calculated using multinomial logistic regression analyses. Adj OR denotes ORs after adjusting for age and gender. The most common genotype was used as the reference genotype. Significant p values are bolded.
| Variables                  | rs9292806 GG (125) | rs9292806 CG (99) | rs9292806 CC (29) | p Value | p adj | rs139013 TT (124) | rs139013 GT (97) | rs139013 GG (29) | p Value | p adj |
|---------------------------|--------------------|------------------|------------------|---------|-------|------------------|------------------|------------------|---------|-------|
| Age (Years)               | 43.5 ± 13.2        | 42.6 ± 12.3      | 44.8 ± 12.2      | 0.72    | -     | 43.1 ± 13.5      | 42.8 ± 12.1      | 44.8 ± 12.3      | 0.75    | -     |
| BMI (kg/m²)               | 28.9 ± 5.7         | 28.4 ± 4.6       | 29.7 ± 4.7       | 0.51    | 0.57  | 28.9 ± 5.7       | 28.3 ± 4.6       | 29.5 ± 4.7       | 0.44    | -     |
| Waist Circumference       | 97.2 ± 12.4        | 93.1 ± 14.2      | 102.8 ± 7.3      | 0.03    | 0.16  | 97.1 ± 12.4      | 93.0 ± 14.1      | 102.7 ± 7.3      | 0.03    | 0.16  |
| SBP (mmHg)                | 123.0 ± 16.0       | 126.0 ± 18.2     | 133.1 ± 21.9 a   | 0.02    | 0.20  | 122.5 ± 17.9     | 126.2 ± 18.3     | 133.5 ± 22.2 a   | 0.01    | 0.16  |
| DBP (mmHg)                | 76.1 ± 9.8         | 78.7 ± 11.4      | 80.3 ± 11.2      | 0.07    | 0.19  | 76.2 ± 9.8       | 78.6 ± 11.7      | 79.9 ± 11.2      | 0.12    | 0.34  |
| Glucose (mmol/L)          | 5.29 ± 0.58        | 5.30 ± 0.63      | 5.75 ± 0.85 a,b  | 0.006   | 0.003 | 5.30 ± 0.58      | 5.42 ± 0.64      | 5.72 ± 0.87 a,b  | 0.013   | 0.009 |
| HbA1c (%)                 | 5.40 ± 0.43        | 5.42 ± 0.45      | 5.75 ± 0.67 a,b  | 0.002   | 0.004 | 5.40 ± 0.43      | 5.41 ± 0.46 a    | 5.76 ± 0.67 a,b  | 0.001   | 0.003 |
| Total Chol (mmol/L)       | 4.91 ± 0.90        | 5.0 ± 0.94       | 5.31 ± 1.06      | 0.16    | 0.20  | 4.92 ± 0.90      | 4.98 ± 0.94      | 5.31 ± 1.06      | 0.17    | 0.22  |
| HDL-Chol (mmol/L)         | 1.50 ± 0.51        | 1.34 ± 0.35 a    | 1.12 ± 0.34 a,b  | 0.001   | 0.02  | 1.49 ± 0.51      | 1.34 ± 0.35 a    | 1.15 ± 0.37 a,b  | 0.002   | 0.03  |
| LDL-Chol (mmol/L)         | 3.12 ± 0.76        | 3.23 ± 0.85      | 3.45 ± 0.92      | 0.17    | 0.29  | 3.13 ± 0.76      | 3.24 ± 0.85      | 3.42 ± 0.95      | 0.25    | 0.37  |
| Triglycerides (mmol/L) #  | 1.29 ± 0.84        | 1.25 ± 0.70      | 1.98 ± 1.41 a,b  | 0.02    | 0.32  | 1.30 ± 0.84      | 1.26 ± 0.71      | 1.90 ± 1.44      | 0.10    | 0.73  |

Data presented as mean ± standard deviation. # denotes values were log-transformed prior to analysis. p adj indicates p values after adjusting for age and gender. Superscript a indicates significantly different from homozygous major genotype group (GG-rs929806 or TT-rs319013). Superscript a,b significantly different from homozygous major and heterozygote genotype groups. Note: Waist circumference data available for 97 participants.
Table 6. Haplotype frequency of *PLCXD3* variants (rs319013, rs9292806) in Control vs. T2DM and Non-MetS vs. MetS subjects.

| Haplotype | Control T2DM | Control T2DM | OR (95 % CI) | p Value |
|-----------|--------------|--------------|--------------|---------|
| TG        | 175          | 222          | 0.68         | 0.73    |
| GC        | 81           | 84           | 0.32         | 0.27    | 0.82 (0.56–1.18) | 0.28 |
| TG        | 252          | 142          | 0.74         | 0.66    |
| GC        | 89           | 73           | 0.26         | 0.34    | 1.46 (1.01–2.14) | 0.047 |

3.1. Association of rs319013 and rs9292806 across GWAS Datasets with T2D and Related Traits

The T2D Knowledge Portal (T2DKP; contains 88 datasets and 198 traits) database (www.type2diabetesgenetics.org) was used to explore GWAS datasets for the association of rs319013 and rs9292806 with T2D and other traits. As shown in Table 7, we detected nominally significant associations \((p < 0.05)\) between the variant allele of *PLCXD3* rs319013 with BMI, creatinine, diastolic blood pressure, eGFR-creat (serum creatinine), HbA1c, height, LDL cholesterol, pericardial adipose tissue volume, triglycerides and T2D in several datasets. However, the most significant associations were observed with BMI \((p < 0.00066)\) in BioBank Japan GWAS, males dataset and T2D \((p < 0.00064)\) in AMP T2D-GENES T2D exome sequence analysis dataset. The variant allele rs9292806 was nominally associated \((p < 0.05)\) with adiponectin, BMI, eGFR-creat, height, pericardial adipose tissue volume, triglycerides, T2D (Table 8). Likewise, the most significant associations of rs9292806 were observed with BMI \((p < 0.0008)\) in BioBank Japan GWAS, male dataset and height \((p < 0.006)\) in GIANT UK Biobank GWAS dataset. These data provide more evidence for the association of rs319013 and rs9292806 in MetS disorders.
### Table 7. Association of rs319013 across all datasets and traits included in the Type2Diabetes knowledge Portal.

| Trait                                      | Dataset                                      | p-Value   | Direction of Effect | Odds Ratio | MA Frequency | Effect   | Samples | References |
|--------------------------------------------|----------------------------------------------|-----------|---------------------|------------|--------------|----------|---------|-------------|
| BMI                                        | BioBank Japan GWAS, males                     | 0.00663   | ↓                   | −0.0132    | 85894        | [17]     |
| Creatinine                                 | GoDartsAffymetrix GWAS                       | 0.044     | ↓                   | −0.0546    | 2917         | [18]     |
| Diastolic blood pressure                   | 13K exome sequence analysis                  | 0.0186    | ↓                   | −0.0326    | 12954        | [19]     |
| eGFR-creat (serum creatinine)              | Hoorn DCS 2018                               | 0.029     | ↓                   | −0.0551    | 3414         | [20]     |
| eGFR-creat (serum creatinine)              | SUMMIT Diabetic Kidney Disease GWAS          | 0.041     | ↓                   | −0.82      | 40340        | [21]     |
| HbA1c                                      | MAGIC HbA1c GWAS: Europeans                  | 0.0425    | ↓                   | −0.0546    | 123665       | [22]     |
| Height                                     | GIANT UK Biobank GWAS                        | 0.0015    | ←                   | 0.0047     | 79564        | [23]     |
| LDL cholesterol                            | BioBank Japan GWAS                           | 0.0455    | ←                   | 0.0105     | 191764       | [17]     |
| Pericardial adipose tissue volume          | VATGen GWAS                                  | 0.012     | ←                   | 0.0085     | 191764       | [17]     |
| Triglycerides                              | BioBank Japan GWAS                           | 0.0485    | ←                   | 0.0085     | 191764       | [17]     |
| Type 2 diabetes                            | AMP T2D-GENES T2D exome sequence analysis    | 0.00642   | ↓                   | 0.954      | 49147        | [19]     |

### Table 8. Association of rs9292806 across all datasets and traits included in the Type2Diabetes knowledge Portal.

| Trait                                      | Dataset                                      | p-Value   | Direction of Effect | Odds Ratio | MA Frequency | Effect   | Samples | References |
|--------------------------------------------|----------------------------------------------|-----------|---------------------|------------|--------------|----------|---------|-------------|
| Adiponectin                                | ADIPOGen GWAS                                | 0.0425    | ←                   | 0.0333     | 0.00976      | 45891    | [15]    |
| BMI                                        | BioBank Japan GWAS, males                     | 0.00898   | ↓                   | 0.433      | −0.0131      | 85894    | [17]    |
| eGFR-creat (serum creatinine)              | Hoorn DCS 2018                               | 0.028     | ↓                   | 0.361      | −0.0573      | 3414     | [20]    |
| eGFR-creat (serum creatinine)              | SUMMIT Diabetic Kidney Disease GWAS          | 0.035     | ↓                   | 0.38       | −0.86        | 4034     | [21]    |
| Height                                     | GIANT UK Biobank GWAS                        | 0.0062    | ←                   | 0.0041     | 795640       | [23]     |
| Pericardial adipose tissue volume          | VATGen GWAS                                  | 0.016     | ←                   | 0.0085     | 191764       | [17]     |
| Triglycerides                              | BioBank Japan GWAS                           | 0.0369    | ←                   | 0.43       | 0.00962      | 191764   | [17]    |
| Type 2 diabetes                            | UK Biobank T2D GWAS                          | 0.032     | ↓                   | 0.977      | 0.4          | 442817   | [24]    |
3.2. Prediction the Effect of rs319013 and rs9292806 on the Function of PLCXD3

To predict the possible consequences of the examined SNPs on the function or expression of the PLCXD3, the chromosomal location for two PLCXD3 variants (rs319013 and rs9292806), reference allele and altered allele were used in online tools “PredictSNP2” (https://loschmidt.chemi.muni.cz/predictsnp2/) [25]. PredictSNP2 is a unified platform for accurately evaluating SNP effects by exploiting the different characteristics of variants in distinct genomic regions. As shown in Figure 4, only rs9292806 showed a deleterious effect on regulatory regions using PredictSNP2, CADD and FATHMM prediction tools with an expected accuracy of 91%, 67% and 82%, respectively.

![Figure 4](image-url)

**Figure 4.** Prediction the effect of the rs9292806 of function and expression of PLCXD3 using the PredictSNP2 platform.

### 4. Discussion and Conclusions

It is well established that MetS increase the risk for cardiovascular disease, T2D and other conditions include dyslipidemia, high blood pressure, excess body fat around the waist and high fasting plasma glucose [26–28]. MetS is ascribed to an interaction between genetic and environmental factors like obesity and lifestyle [29–31]. As the prevalence of MetS disease is expected to escalate globally, identification of genetic markers could be an early prediction to minimize the risk of MetS, T2D and cardiovascular diseases.

In this study, we examined the association of genetic variants of the PLCXD3 gene (rs319013 and rs9292806) with T2D or MetS among UAE nationals. Our results revealed the presence of an association between the homozygous minor genotypes CC-rs9292806 and GG-rs319013 with increased risk of MetS but not T2D (Table 4). GWAS data from T2DKP revealed a significant association of rs9292806 and rs319013 with T2D, BMI and other MetS components in European and Japanese populations (Tables 7 and 8). The finding that both variants have similar association is not surprising as both displayed a very high linkage disequilibrium (Figures 1 and 2).

The association of PLCXD3 variants with fasting glucose or HbA1c in our control subjects (Table 5) is supported by a previously published data set [17,22]. While other reports showed no association
between PLCXD3 (rs319013) with T2D [32,33]. Other datasets indicated a statistically significant association of rs319013 with T2D, as shown in Tables 7 and 8 [19,24,34,35].

To the best of our knowledge, this is the first report investigating the association of genetic variants in the PLCXD3 gene with T2D or MetS, particularly in the UAE population. In a previous study, genetic variants in the PLCXD3 were linked with an early onset bipolar disorder vulnerability and olfactory sensory neurons and CJD [36–38]. The latter finding was disputed by another report [39]. Moreover, a mutation in the PLCXD3 gene was associated with rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomy dysregulation (ROHHAD) [40]. The latter finding is in line with the association of rs319013 and rs9292806 with BMI (Tables 7 and 8).

PI-PLC is an enzyme that hydrolyzes the membrane phospholipid phosphatidylinositol-4, 5-bisphosphate (PIP$_2$) to inositol-1,4,5-trisphosphate (IP$_3$) and diacylglycerol in response to external stimuli such as hormones, neurotransmitters and growth factors [41]. Each PI-PLC subtype contains a well-conserved catalytic domain of separate X- and Y-box. In contrast, the PLXCD isoforms (PLCXD1, PLCXD2 and PLCXD3) have only the catalytic X domain with distinct functions, various tissue distribution and cellular localization [42].

PLCXD3 is highly expressed in human pancreatic islets [10], significantly downregulated in diabetic islets, correlated positively with insulin secretion and negatively with HbA1c as well as BMI [10]. This is in line with our data showing the homozygous genotype of rs9292806 (CC) and rs319013 (GG) have a significantly higher glycemic profile represented by fasting blood glucose and HbA1c in control subjects.

The mechanisms by which these genetic variants affect glucose homeostasis is not clear. However, it can be speculated that these variants influence the expression of PLCXD3, in turn, PLCXD3 affects the glycemic profile. Despite that fact that rs319013 is intronic, it lies at the junction of intron 1 and exon 2 in close proximity to the splice site motifs [36,39]. As exon 2 codes for the active structural domain of PLCXD3 protein, hence any modification to the functioning of the spliceosome at this particular region might impact the activity of the PLCXD3 protein [36,39] and might be influencing the expression of PLCXD3 by altering the mRNA stability or binding of transcription factors. In line with this hypothesis, we showed a bioinformatics tool that rs9292806 influences the regulatory regions of PLCXD3. A possible validation for this finding is to investigate the mRNA expression of PLCXD3 among our participants’ samples with different genotypes. Unfortunately, due to the shortage of RNA materials, we could not perform such analysis.

We believe that it is crucial to replicate the association of the studied variants as well as other variants within the PLCXD3 gene in different ethnic populations. More, the expression level of PLCXD3 needs to be explored in various tissues among different pathological conditions related to metabolic syndrome such as fat, heart, muscle, and brain tissue.

In conclusion, rs9292806 and rs319013 in the PLCXD3 gene are associated with MetS but not T2D in the Emirati population. The finding emphasizes the power of genetic susceptibility to use as biomarkers for prevention strategy of MetS in UAE. Further studies with larger sample sizes and subgroups are warranted for validation and replication.

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Abbreviations

PLCXD3 phosphatidylinositol-specific phospholipase C X domain
HbA1c glycated hemoglobin
T2D Type 2 diabetes
MetS metabolic syndrome
MAF minor allele frequency
BMI body mass index
LDL low-density lipoprotein
HDL high-density lipoprotein
TG triglycerides
CJD sporadic Creutzfeldt-Jakob disease
SNP single-nucleotide polymorphism
SBP systolic blood pressure
DBP diastolic blood pressure

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