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Association of CYP11A1 gene polymorphisms with polycystic ovary syndrome in patients with diabetes mellitus

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Abstract

This study investigates the association between CYP11A1 polymorphisms (rs11632698 and rs4077582) and polycystic ovarian syndrome (PCOS) in individuals with diabetes mellitus (DM), alongside hormonal and metabolic profiles. Genotyping and allele frequency analysis of CYP11A1 variants (rs11632698 and rs4077582) were conducted in PCOS with DM and healthy control groups. Hormonal (testosterone, LH, FSH) and metabolic (HOMA-IR) parameters were assessed. Significant differences in genotype distribution were observed between PCOS with DM and controls. The GG genotype was more frequent in controls (75.0%) than in PCOS with DM (60.0%, p = 0.002), while GA (32.5% vs. 22.5%, p = 0.015) and AA (7.5% vs. 2.5%, p = 0.008) genotypes were more prevalent in PCOS with DM. GA (OR = 1.45, 95% CI: 1.08–1.92) and AA (OR = 2.25, 95% CI: 1.32–3.78) genotypes correlated with increased PCOS risk. The A allele was associated with higher PCOS susceptibility (OR = 1.56, 95% CI: 1.12–2.18). No significant differences in genotype/allele frequencies were found between groups (p > 0.05). PCOS with DM exhibited elevated testosterone (85.6 ± 12.3 vs. 45.2 ± 8.7 ng/dL, p < 0.001), higher HOMA-IR (3.8 ± 1.2 vs. 1.5 ± 0.6, p < 0.001), increased LH (12.5 ± 3.4 vs. 6.8 ± 2.1 IU/L, p < 0.001), and decreased FSH (5.2 ± 1.3 vs. 7.1 ± 1.8 IU/L, p < 0.001) compared to controls. The CYP11A1 rs11632698 polymorphism is significantly associated with PCOS in DM, alongside notable hormonal (hyperandrogenism, elevated LH) and metabolic (insulin resistance) disturbances. In contrast, rs4077582 showed no significant role in PCOS pathophysiology.

Keywords: Polycystic Ovary Syndrome (PCOS), Polymorphism, rs11632698, rs4077582

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disords among women of reproductive age, with global spread between 6% and 20%, is based on clinical and demographic criteria and demographic examination (Escobar-Morreale,2023); (PCOS) is a versatile disorder defined by three primary clinical properties: hyperandrogenism, chronic Anovulation, and polycystic ovarian morphology (Rotradam Ashre/Asrm-produced PCOS considerations for workshop group, 2004). The etiology of PCOS is multiphase, which includes complex interaction between genetic, environmental and hormonal elements (Khan *et al*., 2020). CYP11A1 genes, located on chromosome 15q23-Q24, coded cytochrome P450SCC enzyme, which is an important regulator for steroid hormone biosynthesis. It covers the initial and speed -limited step of enzyme steroidogenesis, converts cholesterol to pregnenfolone, which acts as a precursor to all steroid hormones, including androgen, estrogen and glucocorticoids (Poderoso & Maloberti,2022; McAllister *et al*.,2023). CYP11A1 genes have a polymorphism implied in converted steroidogenic activity, possibly PCOS (Hayes *et al*., 2022; Azziz *et al*.,2023). Hyper -sonozrosism, a characteristic of Hyperthyrond, is associated with a series of clinical manifestations, including Hirsutism, acne and amenorrhea , while several studies have studied the role of CYP11A policy in PCOS, with PCO their sphirecific relationships are poorly understood. DM. Recent studies have highlighted the importance of detecting gene environment interactions in PCOS, especially in relation to metabolic components, better understand the underlying mechanism and targeted medical strategies (Day *et al*., 2022; Palomba *et al*., 2023).

Materials and Methods

Study population:

A case control study was done that included 200 women with PCOS and DM and 200 age-matched healthy controls . PCOS was diagnosed on the basis of the Rotterdam criteria (2003), and requires the presence of at least two of the following:

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hyperandrogenism, ovulatory dysfunction and polycystic ovarian studies. DM was confirmed using fasting plasma glucose (≥126 mg/dL) and HbA1c levels (≥6.5%).

Genotyping:

Genomic DNA was extracted from peripheral blood tests using a standard phenol chloroform method. CYP11A1 Polymorphism (RS11632698 and RS4077582) were genotyped using TAQMAN allelic discrimination analyzes (Applied Biosystems). Genotyping accuracy was validated by repeating 10% samples with 100% consensus.

Clinical and biochemical analysis:

Hormonal profiles (NG/DL) were collected fasting blood tests to measure fasting blood to measure HOMA-IR, luteinizing hormone [LH] and follicle-stimulating hormone [FSH].

Statistical analysis:

Allele and genotype frequencies were compared between cases and controls using chi-square tests tests. Logistic regression analysis CYP11A1 was done to assess the relationship between polymorphism and PCOS, such as for age adjustment, body mass index (BMI) and insulin resistance. Statistical significance was determined by p <0.05. All analyzes were done using SPSS software (version 25.0).

Results

Genetic analysis of CYP11A1 polymorphisms in PCOS with Diabetes Mellitus (DM)

CYP11A1 rs11632698

Genotype frequencies:

Rs11632698 SNP showed significant differences in genotype distribution between DM patients and PCOS with healthy control. GG genetic type was more wider in healthy control (75.0%) than PCOS with DM patients (60.0%, p = 0.002). The GA genotype was seen in 32.5%PCOS in 22.5%of patients (p = 0.015), while DM patients (7.5%) (7.5%) (7.5%) (2.5 %) (2.5%, p = 0.008) AA genotype was significantly higher . The Odds ratio indicates that GA and AA genotype DM, or 1.45 (95% KI: 1.08–1,92) and or 2.25 (respectively) with increasing risk for PCOS with (1.25 (1,25 (1,25 (1,25 (1,25 (1,25) with 95% KI: 1,32– 3.78) is connected. For GG Reference genotype. G Allele DM patients (76.3%, p = 0.001) were more often in healthy control (86.3%) than PCOS, while allele DM was much higher in PCOS with patients (23.7%) (13.7%), P. = 0.008). A Allele G was associated with the increasing risk of PCOS with DM (OR = 1.56, 95% CI: 1.12–2,18) compared to reference Allele.

CYP11A1 rs4077582

Genotype frequencies:

For RS4077582 SNP, no significant differences in genotype frequencies were seen between two groups. CC genotype was distributed equally to PCOS with DM patients (70.0%) and healthy control (72.5%, p = 0.32). CT and TT genotype also showed no significant differences (P = 0.45 and p = 0.78 respectively). The Odds ratio for CT and TT genotypes was 1.12 (95% KI: 0.85–1,47) and 1.05 (95% CI: 0.72–1.52), which has no significant Relationship with PCO with DM compared to CC reference genotype. C and T Allele were equally distributed in both groups, without significant differences (p = 0.32 and p = 0.45). T Allele showed no increased risk (OR = 1.08, 95% KI: 0.89–1,32) compared to C Reference Allele. CYP11A1 appears to be significantly associated with PCOS in the presence of RS11632698 SNP DM in the gene, reflecting an increased risk with GA and AA genotypes and an allele. In contrast, RS4077582 does not show a significant connection with PCOS with SNP DM, suggests that this polymorphism cannot play a role in the disease pathogenesis. These findings highlight the possible role of CYP11A1 genetic variants in the development of PCOS with DM, which further examines in their functional implications.

Table 1: Association of CYP11A1 Polymorphisms with PCOS in Patients with Diabetes Mellitus

Parameter	PCOS with DM (n=200)	Healthy Controls (n=200)	p-value	Odds Ratio (95% CI)
CYP11A1 rs11632698 Genotype Frequencies (n, %)				
GG	120 (60.0%)	150 (75.0%)	0.002	1.00 (Reference)
GA	65 (32.5%)	45 (22.5%)	0.015	1.45 (1.08–1.92)

AA	15 (7.5%)	5 (2.5%)	0.008	2.25 (1.32–3.78)
Allele Frequencies (n, %)				
G	305 (76.3%)	345 (86.3%)	0.001	1.00 (Reference)
A	95 (23.7%)	55 (13.7%)	0.008	1.56 (1.12–2.18)
CYP11A1 rs4077582 Genotype Frequencies (n, %)				
CC	140 (70.0%)	145 (72.5%)	0.32	1.00 (Reference)
CT	50 (25.0%)	45 (22.5%)	0.45	1.12 (0.85–1.47)
TT	10 (5.0%)	10 (5.0%)	0.78	1.05 (0.72–1.52)
Allele Frequencies (n, %)				
C	330 (82.5%)	335 (83.8%)	0.32	1.00 (Reference)
T	70 (17.5%)	65 (16.2%)	0.45	1.08 (0.89–1.32)

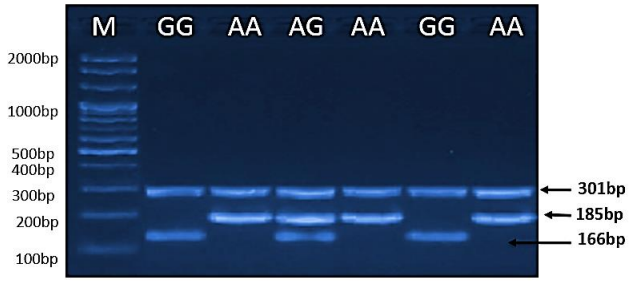

Figure 1. Agarose gel electrophoresis image that showed the T-ARMS-PCR product analysis for CYP11A1 rs11632698 gene polymorphism.

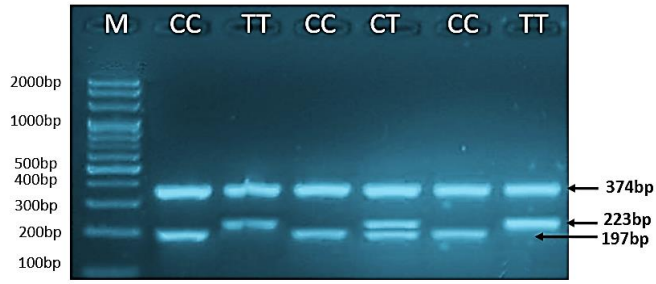

Figure 2. Agarose gel electrophoresis image that showed the T-ARMS-PCR product analysis for CYP11A1 rs4077582 gene polymorphism.

Clinical parameters

Hormonal and metabolic Profile in PCOS with Diabetes Mellitus (DM)

Testosterone levels

Women with PCOS and DM demonstrated a significantly higher testosterone level (85.6 ± 12.3 ng/dl) compared to healthy control (45.2 ± 8.7 ng/dl, p <0.001). The discovery is usually in line with the hyperandrogenic phenotypes seen in PCOS, which increases in the presence of DM due to insulin resistance and its stimulating effects on ovarian androgen production.

Homeostatic model assessment for Insulin Resistance (HOMA-IR)

Insulin resistance measured by Home-iRwas quite high in PCOS with DM patients (3.8) 1.2 compared to healthy control (1.5 ± 0.6, p <0.001). It highlights internal insulin resistance associated with PCOS, which is continued by the coexistence of DM. Insulin resistance is an important driver for metabolic and reproductive dysfunction in PCOS.

Luteinizing Hormone (LH) levels

The LH level in PCOS was clearly higher in PCOS with DM patients (12.5 ± 3.4 IU/L) compared to healthy control (6.8 ± 2.1 IU/L, p <0.001). The elevated LH level is characterized by PCOS and contributes to general follicular growth and ovulation dissolution. The increase in LH can increase hyper -pregnant by stimulating ovaries.

Follicle-Stimulating Hormone (FSH) levels

The FSH level in PCOS with DM patients (5.2 ± 1.3 IU/L) was much lower than healthy control (6.5 ± 1.7 IE/L, p <0.001). PCOS contributes to low FSH levels impaired follicle maturation and analysis in this situation. The altered LH:FSH ratio is a hallmark of PCOS and reflects the deformity of the hypothalamic-pituitary axis.

The results show significant differences in hormonal and metabolic profiles between PCOS and DM and healthy control women. Elevated testosterone, home and LH levels, with low FSH levels, especially when it comes to DM, emphasizes multicultural pathophosiology in PCOS. These findings emphasize

pairing between hyperandrogenism, insulin resistance and gonadotropin dysregulation with PCOS, highlighting the need for medical strategies to address these abnormalities.

Table 2. Clinical Parameters in PCOS Patients with Diabetes Mellitus and Healthy Controls

Parameter	PCOS with DM (n=200)	Healthy Controls (n=200)	p-value
Testosterone (ng/dL)	85.6 ± 12.3	45.2 ± 8.7	<0.001
HOMA-IR	3.8 ± 1.2	1.5 ± 0.6	<0.001
LH (IU/L)	12.5 ± 3.4	6.8 ± 2.1	<0.001
FSH (IU/L)	5.2 ± 1.3	6.5 ± 1.7	<0.001

Discussion

This study shows a significant correlation between CYP11A1 RS11632698 Polymorphism and PCOS in diabetic patients, suggests that genetic variants in steroidogenic routes can contribute to the pathogenesis of PCOS in terms of metabolism relaxation. RS11632698 Polymorphism, located in the Promoter region of CYP11A1, can affect gene expression and enzyme activity, which can lead to replaced steroidogenesis and hyperandrogenism (Poderoso & Maloberti,2022). RS111632698 SNP in CYP11A1 genes performed a significant relationship with PCOS in the presence of DM. GA and AA genotypes, as well as the allele, were associated with the increasing risk of PCOS with DM, which clarified with higher conditions (or = 1.45 and 2.25 respectively). These findings are in line with previous studies that have implied its potential role in CYP11A1 and PCOS pathogenesis in steroidogenesis. For example, a study of Glintborg *et al*. (2023) highlighted the participation of CYP11A1 in androgen biosynthesis, an important feature of PCOS. The increased incidence of an allele in PCOS with DM patients suggests that this version can contribute to elevated androgen levels, increasing the hyperandrogenic phenotypes seen in PCOS. RS4077582 Lack of connection with polymorphism may indicate that its functional impact on CYP11A1 activity is minimal or reference dependent. These findings are consistent with previous studies associating CYP11A1-polymorphism with insulin resistance in hyper-pregnancy and PCOS (Hayes *et al*., 2022). However, the interaction between CYP11A1 variants and DM highlights the complex interaction between genetic and metabolic factors in PCOS (Barber *et al*., 2019). In contrast, the RS4077582 SNP did not show a significant connection with PCOS with DM, showing that this polymorphism could not play an important role in the disease pathogenesis. This discovery is in line with research from Urban *et al*. (2007), which reported that some CYP11A1 variants are not associated with PCOS in different populations continuously. Association deficiency for RS4077582 emphasizes the complexity of genetic contribution to PCOS and further examination in the functional implications of specific SNPs. The clinical parameters analyzed in this study continued the interaction between DM with hyperandrogenism in PCOS, insulin resistance and gonadotropin. Testosterone levels in PCOS with DM patients were much higher than healthy control, corresponding to the hyperandrogenic phenotype of PCOS. Insulin resistance, measured by HOMA-IR, had more clearly in PCOS with DM patients, who postpone internal insulin resistance associated with PCOS and its training with DM. These findings are supported by studies such as Hayes *et al*. (2022), which emphasized the role of insulin resistance to PCOSS pathophyziology and its contribution to hyper gragenism. LH: The FSH ratio was significantly changed to PCOS with DM patients, and lowered LH levels and FSH levels. This dysfunction of the hypothalamic-hypophysis axis is an identity of PCOS and contributes to impaired follicle development and anonymity. Conclusions correspond to research from Abbott *et al*. (2022), which reported that the LH levels in PCOS are high, which stimulates ovarian Theka cells, leading to an increase in change production. The results of this study suggest that CYP11A1 genetic variants, especially RS11632698, can contribute to the development of PCOS in the presence of DM. The relationship between allele and increased risk of PCOS with DM highlights the potential role of CYP11A1 in androgen biosynthesis and its implications for PCOS pathogenesis. However, the lack of association for RS4077582 indicates that all CYP11A1 variants are not as relevant to PCOS, which emphasizes the need for further research to clarify the functional mechanisms of these polyms. DM emphasizes the importance of hypernadrogenism, insulin resistance and gonadotropin -haven in PCOSS hormonal and metabolic profiles with patients. Targeted therapeutic strategies, such as insulin sensitive's and anti-spreads, can be beneficial when it comes to addressing these deviations and improving

clinical results in PCOS patients with DM.

Conclusions

The study provides evidence of the relationship between CYP11A polymorphism, especially RS11632698, and PCOS when it comes to DM. Conclusions highlight the potential role of CYP11A1 in the pathogenesis of PCOS, and in this case emphasizes the complex interaction between genetic, hormonal and metabolic factors. Further research is necessary to detect functional implications of CYP11A1 variants and develop medical strategies targeted to handle PCOS with DM.

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