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# Correlation of DENND1A gene polymorphism with polycystic ovary syndrome in Iraqi women

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**Abstract:**
One of the most common endocrine conditions affecting women is polycystic ovarian syndrome (PCOS), which has complex genetic background.It has been proposed that the DENND1A gene, specifically the single nucleotide polymorphism (SNP) rs2479106, is involved in the pathophysiology of PCOS. The purpose of this study was to investigate the relationship between Iraqi women's susceptibility to PCOS and the DENND1A rs2479106 polymorphism.
Between September 2025 and March 2026, a case-control research was carried out with 50 women who met the Rotterdam criteria for PCOS diagnosis and a control group of 25 age-matched, healthy women. Hormone levels and anthropometric parameters were also assessed in both groups. PCR and Sanger sequencing were used to genotype the DENND1A rs2479106 polymorphism.
Overall, PCOS patients exhibited significantly higher LH levels, LH/FSH ratio, and testosterone levels compared with controls, while FSH and prolactin levels showed no significant differences between the two groups At the genetic levelThree genotypes were identified : AA, AG, and GG. The heterozygous AG genotype was associated with the risk of illness (p = 0.0042, OR = 1.29) and was substantially more common in PCOS patients (54.00%) than in controls (28.00%). PCOS patients had a lower frequency of the GG genotype (12%) than controls (16%), although this

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difference was not statistically significant (OR=0.673, p=0.237). At the allelic level, the frequency of the G allele was significantly higher in PCOS patients (0.39) compared with controls (0.30) (Chi-square = 4.758, P = 0.0488), while the A allele was more prevalent among controls (0.70) than patients (0.61) (Chi-square = 4.793, P = 0.0485).

In conclusion, our findings suggest a potential association between the DENND1A rs2479106 polymorphism, particularly the heterozygous AG genotype, and PCOS susceptibility in Iraqi women. Given the limited sample size, further studies with larger cohorts are needed to confirm these findings.

**Keywords***:* DENND1 gene , PCOS, DNA sequencing ,rs2479106 polymorphism

## Introduction

Polycystic ovary syndrome (PCOS) is a prevalent and diverse endocrine condition impacting women of reproductive age, defined by a combination of hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology observed via ultrasound. In addition to its reproductive consequences, PCOS is now acknowledged as a systemic disorder linked to significant metabolic, cardiovascular, and psychiatric comorbidities. **(Teede *et al.*, 2023).** It is estimated to affect 4–10% of women of reproductive age worldwide **(Singh et al., 2023)** with ovarian dysfunction being a central feature while its exact etiology remains largely unclear **(Zhu and Goodarzi, 2022; Moran and Teede, 2009)**PCOS is considered a polygenic and multifactorial disorder influenced by multiple genetic and environmental factors rather than a single gene defect **(Nautiyal *et al.*, 2022).** A number of genes have been studied in relation to PCOS, including those involved in ovarian and adrenal steroidogenesis, gonadotropin regulation, insulin signaling, energy homeostasis, and chronic inflammation **(Sharma *et al.*, 2023; Wang *et al.*, 2012)**. Of these, genes involved in androgen biosynthesis regulation and intracellular trafficking have been increasingly focused as possible players in the pathogenesis of PCOS. It has been suggested that

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the DENN domain-containing 1A (DENND1A) gene may be associated with PCOS **(Dapas *et al.*, 2019)**. DENND1A belongs to the connecdenn family of genes, encodes a protein that participates in clathrin-mediated endocytosis, and acts as a guanine nucleotide exchange factor for Rab35 in endosomal membrane trafficking **(Allaire *et al.*, 2010; Marat *et al.*, 2011)**. Importantly, this trafficking role is believed to affect androgen biosynthesis in theca cells, which may be a factor in the hyperandrogenism seen in PCOS. The DENND1A gene resides on chromosome 9 (9q22.32) and encodes two major isoforms (variant 1 and variant 2) that are differentially expressed in theca cells of women with PCOS, suggesting a direct mechanistic link to the pathophysiology of the disease **(Tee *et al.*, 2016; Teves *et al.*, 2020).** In genome-wide association studies of Chinese populations, single

nucleotide polymorphisms (SNPs) in the DENND1A gene were identified, including rs2479106 **(Chen *et al.*, 2011).** The rs2479106 variant lies in a non-coding, intronic region of DENND1A, suggesting a regulatory rather than structural effect. It is thought to be linked to increased expression of the DENND1A.V2 isoform, which acts as a Rab-GTPase exchange factor regulating receptor endocytosis **(Hutagalung & Novick, 2011).** Elevated DENND1A.V2 upregulates CYP17A1 and CYP11A1, driving excess androgen biosynthesis in theca cells — a hallmark of PCOS **(McAllister *et al.*, 2014).**Although the association between the DENND1A rs2479106 polymorphism and PCOS has been investigated in different populations **(Gao *et al.*, 2016).,** the reported findings remain inconsistent across ethnic groups. Furthermore, only one previous study has examined this association in the Iraqi population, highlighting the need for additional replication studies to validate the findings and strengthen the available evidence. Therefore, the present study aimed to investigate the association between the DENND1A rs2479106 polymorphism and susceptibility to PCOS among Iraqi women.

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**previous studies**

**1.(Hakami et al., 2025)**

**Title:** Genotypes of Single-nucleotide polymorphisms on DENND1A in an association with polycystic ovary syndrome among Saudi Arabian females**. Summary:** A case-control research genotyped rs2479106 via DNA sequencing in 33 PCOS and 36 healthy Saudi females, demonstrating a significant correlation between rs2479106 and heightened susceptibility to PCOS in Saudi Arabian women**.**

**2.(Bao et al., 2016)**

**Title:** Association of DENND1A Gene Polymorphisms with Polycystic Ovary Syndrome: A Meta-Analysis.

**Summary**

Bao et al. conducted a meta-analysis including eight independent studies comprising 8,185 women with PCOS and 28,675 healthy controls to evaluate the association between DENND1A polymorphisms and PCOS. The analysis showed that the heterozygous AG genotype of rs2479106 was significantly associated with an increased risk of PCOS, particularly in Asian populations, whereas no significant association was detected among Caucasian populations. These findings indicate that the effect of rs2479106 on PCOS susceptibility may vary according to ethnic background and genetic diversity.

**3. (Gammoh et al., 2015)**

**Title**: DENND1A gene variants in Bahraini Arab women with polycystic ovary syndrome.

**Summary**

Gammoh et al. performed a case–control study involving 191 Bahraini women with PCOS and 202 healthy controls to investigate the association between DENND1A polymorphisms, including rs2479106, and PCOS. Genotyping was carried out using real-time PCR. Unlike several studies conducted in Asian populations, the authors did not observe a significant association between rs2479106 and PCOS susceptibility in Bahraini women. They concluded that the influence of DENND1A polymorphisms

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may differ among ethnic populations and emphasized the need for further studies in different genetic backgrounds.

## Materials and Methods

### Study subject

This case-control research inclued75 women aged between 18 and 45 years in both groups. The study was conducted between September 2025 and- March 2026. ~~The~~ Samples were collected at AL-Elwiya Educational Hospital. The study included 50 individuals diagnosed with PCOS, and 25 healthy women constituted the control group. PCOS diagnosis was based on the Rotterdam criteria **(Christ and Cedars, 2023).** The diagnosis was established when at least two criteria were satisfied (oligo/anovulation, hyperandrogenism, or polycystic ovaries via ultrasound), individuals with hypertension, diabetes, and a body mass index (BMI) exceeding 35 kg/m² were omitted from the study.

### Collection of Blood Samples

Five milliliters of venous blood were collected from all women on days 2 to 3 of their menstrual cycles. The sample was partitioned into 2 ml of ethylenediaminetetraacetic acid (EDTA) and 3 ml gel tubes.

### Biochemical and Endocrine Assessment

Serum was extracted from coagulated blood for hormonal analysis and quantified using the Roche/Hitachi Cobas C111 equipment in accordance with established protocols.

### DNA Extraction

Genomic DNA was isolated from EDTA-treated blood samples utilizing a commercial DNA extraction kit (gSYNC™ DNA Mini Kit Whole Blood Protocol, Geneaid, Korea) in accordance with the manufacturer's guidelines.

### Polymerase Chain Reaction (PCR) amplification

Using special primers created for this investigation by Macrogen Company (Korea), the targeted region which includes the rs2479106 polymorphism of DENND1A was amplified. RS-106 Forward (5'-

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GTGCTGGATATACAACACTGA-3') is the forward primer sequence, while RS-106 reverse (5'-TCTCTACTCCCCTACATGAG-3') is the reverse primer. The stock solution, which had a final concentration of 100 pmol/µl, was made by dissolving lyophilized primers in nuclease-free water according to the manufacturer's instructions. 90µl of nuclease-free water was combined with 10µl of primer stock solution, which was stored at -20°C in the freezer, to produce a feasible primer solution of 10pmol/µl. The PCR was performed by using the Thermal Cycler (Thermo Fisher Scientific, USA). 8.5 µl of Nuclease Free Water, 12.5 µl of Go Taq Green Master Mix (Promega, USA), 2 µl of template DNA, and 1 µl of each forward and reverse primer made up the entire volume (25 µl) of the PCR reaction mixture. Three minutes of initial denaturation at 95 °C, followed by forty cycles of denaturation at 94°C for thirty seconds, then thirty seconds of annealing at 58 °C, followed by forty-five seconds of extension at 72 °C, and concluding with five minutes of final extension at 72 °C were the cycling conditions used to the DENND1A gene. The PCR amplification was verified by electrophoresis on a 1 using a DNA ladder (100–1200 bp) supplied by Promega (USA). 1.5% agarose gel stained for 60 minutes at 100 volts/mAmp using 1 µl (10 mg/ml) ethidium bromide in 1X TAE buffer (Promega, USA). DNA samples were visible when seen under a UV-trans illuminator with 669bp product size.

**Sanger Sequencing**

PCR products of the amplified gene area from all patient and control samples were dispatched to Macrogen (Korea) for Sanger sequencing utilizing the forward primer. The acquired sequencing data were matched with GenBank reference sequences to detect the existence of single nucleotide polymorphisms (SNPs). Sequence analysis was conducted utilizing Geneious software.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Mean ± SD values and compared with the independent samples t-test. The chi-square

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used in order to compare the allele frequencies and genotypes. The relationship between the odds ratio of having PCOS and the rs2479106 was determined. A p-value ($P < 0.05$) was statistically significant.

## Results and Discussions

### Clinical and hormonal characteristics

Most demographic and clinical variables were higher in patients with PCOS compared with controls; however, not all differences reached statistical significance. The age difference between the two groups was not statistically significant ($P > 0.05$), with a mean age of 26.48 ± 0.75 years in the PCOS group and 24.12 ± 0.99 years in the control group (Table 1). Similarly, no significant association was observed between BMI values of PCOS patients (23.44 ± 0.45 kg/m²) and healthy controls (22.34 ± 0.36 kg/m²) ($P > 0.05$). This finding is consistent with a European study by (Brower *et al*.,2019), which reported no significant variation in BMI values or weight categories (normal, overweight, obese) between PCOS patients and controls.

**Table (1) Demographic, clinical, and hormonal characteristics of study groups**

| | | | |
|---|---|---|---|
| Age (year) | 26.48 ±0.75 | 24.12 ±0.99 | 0.0701 |
| BMI ($Kg/m^2$) | 23.44 ±0.45 | 22.34 ±0.36 | 0.1118 |
| LH (mIU/ml) | 10.93 ±0.15 | 5.91 ±0.07 | 0.0001 |
| FSH (mIU/ml) | 6.205±0.75 | 6.074 ±0.31 | 0.9040 |
| LH/FSH ratio | 1.809 ±0.02 | 1.182 ±0.02 | 0.0001 |
| Prolactin (ng/ml) | 14.89 ±0.54 | 14.92 ±0.52 | 0.9756 |
| Testosterone (ng/ml) | 0.837 ±0.12 | 0.173 ±0.01 | 0.0003 |

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In contrast, LH levels, the LH/FSH ratio, and testosterone levels were significantly elevated in PCOS patients compared with controls ($P < 0.05$), as shown in Table 1. These findings are consistent with previous reports **(Shaheed et al., 2021; Al-Fartosy et al., 2020; Mirza et al., 2022)**. Conversely, FSH and prolactin levels showed no statistically significant difference between the two groups, in agreement with the findings of **(Al-Lami *et al*., 2020)** and **(Szosland *et al*., 2015).**

The elevated LH, LH/FSH ratio, and testosterone levels observed in PCOS patients—despite comparable FSH and prolactin levels—may serve as useful discriminating markers for differential diagnosis. The multifactorial etiology of PCOS, which combines a hereditary genetic basis with environmental and lifestyle influences, may account for the observed variability in hormonal and clinical presentation across studies.

**PCR Amplification and Sequencing Examination**

The amplified DENND1A gene region's PCR products were examined via agarose gel electrophoresis to verify the successful amplification of the target fragment (669 bp). The amplified products were then sequenced using the Sanger method to detect any differences in the nucleotides of the study samples. The sequencing data was used to identify and confirm the presence/absence of different genotypes (AA, AG, GG) of the polymorphism rs2479106 as shown in Figures (1) and (2).

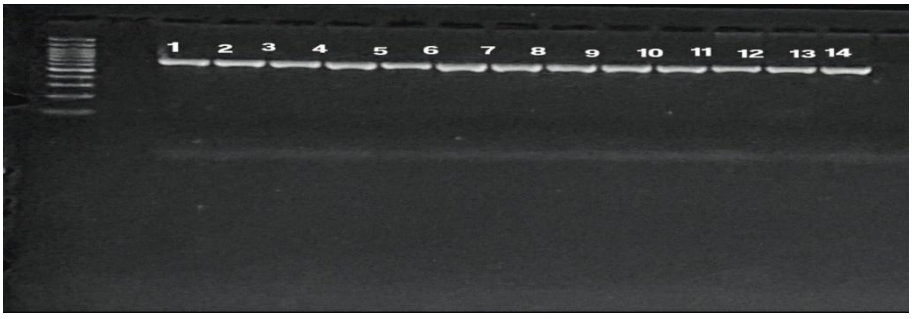


**Figure 1. Agarose gel 1.5% showing PCR products with DENND1A gene (669 bp)**

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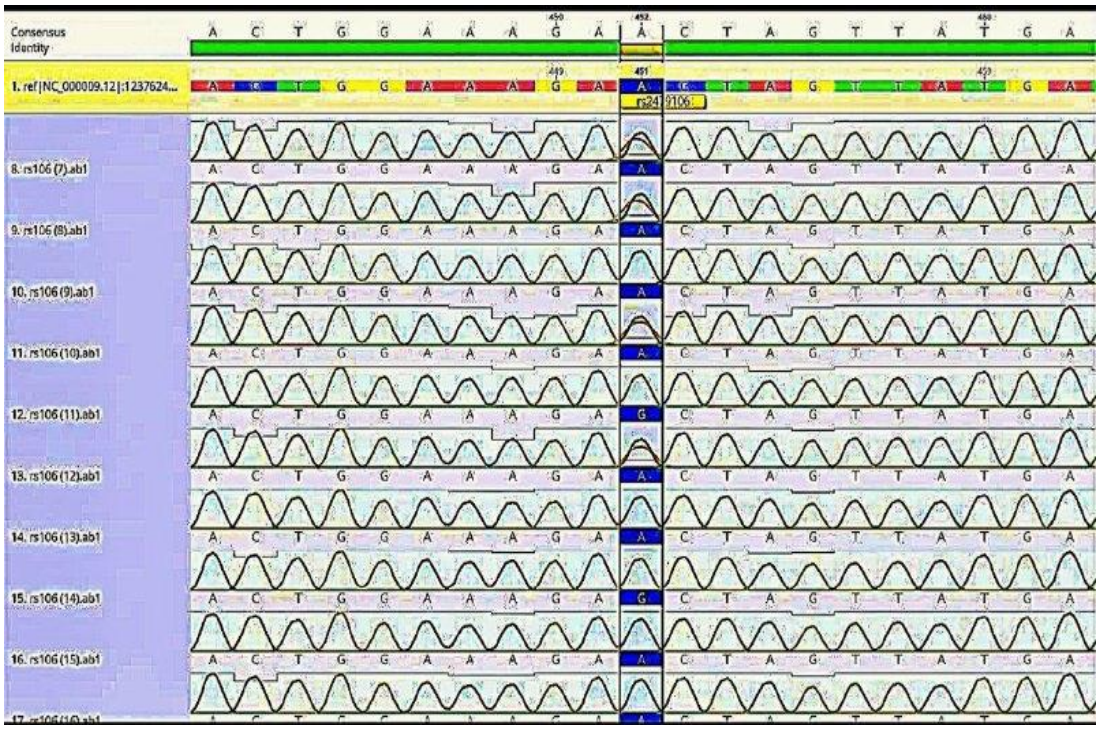


**Figure2. DNA Sequence Chromatogram of the DENND1A Gene SNP Site (A>G: rs2479106).**

## Genotype and allele distribution

The genotype distribution of the DENND1A rs2479106 polymorphism in the study group comprised three genotypes: homozygous wild-type (AA), heterozygous (AG), and homozygous variant (GG) (Table 2).

The heterozygous AG genotype was significantly more frequent in PCOS patients (54.00%) than in controls (28.00%) (Chi-square = 9.428, P = 0.0042; OR = 1.29, 95% CI: 0.94–2.16), suggesting a possible association with increased disease susceptibility. The homozygous AA genotype, used as the reference (OR = 1), was less prevalent in patients (34.00%) than in controls (56.00%) (Chi-square = 4.29, P = 0.0429). No significant difference was observed for the homozygous GG genotype between patients (12.00%) and controls (16.00%) (Chi-square = 0.784, P = 0.237; OR = 0.673, 95% CI: 0.41–0.80)

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At the allelic level, the G allele was significantly more common among PCOS patients than controls, supporting its role as a risk allele. Taken together, the overrepresentation of the heterozygous AG genotype—together with the non-significant association observed for the homozygous GG genotype—is consistent with a heterozygote-advantage inheritance model, in which a single copy of the G allele may be sufficient to confer increased disease risk. The lack of significance for the GG genotype may be attributable to the limited sample size, which reduces statistical power to detect moderate effect sizes.

**Table 2: Genotype distribution and allele frequency of *DENND1A* (A>G) in study groups**

| Genotype/ | Patients No. (%) | Control No. (%) | Chi-Square | P-value | O.R. (C.I) |
|---|---|---|---|---|---|
| AA | 17 (34.00%) | 14 (56.00%) | 4.291 * | 0.0492 | Ref.=1 |
| AG | 27 (54.00%) | 7 (28.00%) | 9.428 ** | 0.0042 | 1.29 (0.94-2.16) |
| GG | 6 (12.00%) | 4 (16.00%) | 0.784 NS | 0.237 | 0.673 (0.41-0.80) |
| Total | 50 | 25 | | | |
| Allele | Frequency | | --- | | |
| A | 61 (0.61) | 35 (0.70) | 4.793 | 0.0485 * | 0.866 (0.62-1.27) |
| G | 39 (0.39) | 15 (0.30) | 4.758 | 0.0488 * | 0.832 (0.59-1.22) |
| * (P≤0.05), ** (P≤0.01). | | | | | |

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The current study agree with previous studies conducted in different populations **(Hakami *et al*., 2025; Xia *et al*., 2019; Bao *et al*., 2016)** finding by Cui et al. could not directly assess the risk of PCOS; however, they indicated that the AG+GG genotypes of rs2479106 were substantially correlated with elevated 2-hour post-load insulin levels in PCOS patients (p = 0.02) ***(Cui et al., 2013)***. These findings reinforce the potential metabolic implications of the G allele and highlight its prospective clinical significance.

Contrary to the current findings, a study in Bahrain **(Gammoh *et al*., 2015)** found no significant correlation between rs2479106 and susceptibility to PCOS. Additionally, a Danish Caucasian cohort study indicated that the G gene may confer a protective benefit against PCOS **(Eriksen *et al*., 2012).**Discrepancies among studies may indicate ethnic differences, genetic heterogeneity, environmental factors , and variations in sample size .

The mechanism explains this SNP that rs2479106 (G allele) may increase PCOS susceptibility by enhancing androgen production the SNP localized in intron 4 of the gene, it affects gene expression in ovarian theca cells via Rab35-GTpases, without altering protein structure. substitution of A by G increase androgen production raising PCOS risk (**Eriksen *et al*., 2012; Strauss *et al*., 2012; Hutagalung and Novick, 2011).**

## Conclusion

According to the current study, Iraqi women who are predisposed to polycystic ovarian syndrome (PCOS) are linked to the DENND1A gene rs2479106 polymorphism. The findings indicate that the genotype and allele frequencies of patients and controls differ significantly.

## Ethics

All experimental research was conducted at Al-Mustansiriya University, specifically in the College of Science, Department of Biology, and received approval from the Research Ethics Committee. Ethics approval number is BCSMU/10025/0082Z. All collected information was kept strictly confidential.

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# ارتباط تعدد أشكال جين DENND1A بمتلازمة تكيس المبايض لدى النساء العراقيات

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**مستخلص البحث:**

تُعد متلازمة تكيس المبايض (PCOS) من أكثر اضطرابات الغدد الصماء شيوعًا التي تصيب النساء، وهي حالة ذات خلفية وراثية معقدة. وقد اقتُرح أن جينDENND1A ، وبالتحديد تعدد أشكال النوكليوتيد المفرد (SNP) rs2479106، يشارك في الآلية المرضية لمتلازمة تكيس المبايض.هدفت هذه الدراسة إلى تقصي العلاقة بين تعدد الأشكال الوراثي DENND1A rs2479106وقابلية الإصابة بمتلازمة تكيس المبايض لدى النساء العراقيات. أجريت دراسة حاله مراقبه خلال الفترة الممتدة من سبتمبر 2025 إلى مارس 2026، وشملت 50 امرأة شُخِّصن بمتلازمة تكيس المبايض وفقًا لمعايير روتردام، بالإضافة إلى مجموعة ضابطة مكونة من 25 امرأة سليمة ومتقاربة في العمر. كما جرى تقييم مستويات الهرمونات والقياسات الأنثروبومترية لدى المجموعتين. وتم تحديد الأنماط الجينية لتعدد الأشكال الوراثي DENND1A rs2479106باستخدام تقنية تفاعل البوليميراز المتسلسل (PCR) وتسلسل سانغر.(Sanger sequencing) أظهرت النتائج أن مريضات متلازمة تكيس المبايض سجلن مستويات أعلى بشكل معنوي من الهرمون اللوتيني(LH) ، ونسبة LH/FSH، ومستويات هرمون التستوستيرون مقارنة بالمجموعة الضابطة، في حين لم تُسجل فروق ذات دلالة إحصائية في مستويات الهرمون المنبه للجريب (FSH) أو هرمون البرولاكتين بين المجموعتين. وعلى المستوى الوراثي، تم تحديد ثلاثة أنماط جينية هي AA :و AGو GG.وكان النمط الجيني غير المتماثل AGأكثر شيوعًا بشكل ملحوظ لدى مريضات متلازمة تكيس المبايض (54.00%) مقارنة بالمجموعة الضابطة (28.00%)، وارتبط بزيادة خطر الإصابة بالمرض(p = 0.0042 ، (OR = 1.29).في المقابل، كان تكرار النمط الجيني GGأقل لدى المريضات (12%) مقارنة بالمجموعة الضابطة (16%)، إلا أن هذا الفرق لم يكن ذا دلالة إحصائية (OR = 0.673 =، p = 0.237). أما على مستوى الأليلات، فقد كان تكرار الأليل Gأعلى بشكل معنوي لدى مريضات متلازمة تكيس المبايض (0.39) مقارنة بالمجموعة الضابطة(Chi-square = 4.758 (0.30) ، P = (0.0488، في حين كان الأليل Aأكثر شيوعًا لدى المجموعة الضابطة (0.70) مقارنة بالمريضات (0.61) (Chi-square = 4.793، P = 0.0485). في الختام، تشير نتائج هذه الدراسة إلى وجود ارتباط محتمل بين تعدد الأشكال الوراثي DENND1A rs2479106، ولا سيما النمط الجيني غير المتماثل AG، وقابلية الإصابة بمتلازمة تكيس المبايض لدى النساء العراقيات. ونظرًا لمحدودية حجم العينة، فإن هناك حاجة إلى إجراء دراسات مستقبلية تشمل أعدادًا أكبر من المشاركات لتأكيد هذه النتائج.

**الكلمات المفتاحية**: جين DENND1A، متلازمة تكيس المبايض، تسلسل الحمض النووي، تعدد الأشكال الجينية rs2479106 ملاحظة : هل البحث مستل من رسالة ماجستير او اطروحة دكتوراه ؟ نعم : كلا :