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Original Research Article

Aromatase Gene Polymorphisms at the Rs10046 Position and Their Relationship to Certain Biochemical Variables in Women with Polycystic Ovary Syndrome

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Abstract: The aim of this study is to investigate the relationship between single nucleotide polymorphisms (SNPs) at the rs10046 locus in the aromatase gene CYP19A1 and certain biochemical variables, and their connection to the occurrence of polycystic ovary syndrome (PCOS). Ninety (90) samples, aged 16-45 years, were collected for this study between November 1, 2022, and March 1, 2023. The samples were divided into two groups: 60 patients and 30 healthy individuals. Samples were collected from gynecology clinics at Tikrit Teaching Hospital and outpatient gynecology clinics. The results showed a significant increase in LH concentrations in patients compared to healthy individuals across all genotypes. The highest mean LH concentration was 18.97 in patients with the GG genotype, while the lowest mean LH concentration was 6.57 in healthy individuals with the GL genotype, While no significant differences were observed between the genotypes in the healthy group, as all were within the normal range for LH, a high standard deviation was noted in the GL and GG genotypes among the patients. This indicates a significant variation in the severity of hormonal imbalance between cases, which is common in polycystic ovary syndrome (PCOS) due to varying degrees of hypothalamic hyperactivity in the brain. The results also suggest that the presence of the G allele in the GL and GG genotypes may be associated with increased activity of the hormonal pathways regulating LH secretion or with increased ovarian sensitivity to it. The LH/FSH ratio showed a gradual increase from the AA genotype (2.51 ± 2.93) to the GA genotype (3.33 ± 2.81) and then to the GG genotype (3.90 ± 4.94): AA → GA → GG. In contrast, the control group showed proportions within physiological limits, with mean values of 0.91 ± 0.35, 1.18 ± 0.50, and 1.49 ± 0.46 for AA, GA, and GG genotypes respectively. These results support the multifactorial nature of polycystic ovary syndrome, which includes both genetic predisposition and hormonal changes.

Keywords: Aromatase Gene, PCOS, rs10046.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common hormonal disorders affecting women of reproductive age, impacting fertility both during and after menopause (Hanan *et al*., 2020). This syndrome is defined as a complex, heterogeneous hormonal disorder affecting more than 7% of women of reproductive age (Diamanti-Kandarakis, 2008). Its global prevalence is estimated to be approximately 5–10%, depending on the diagnostic criteria (Deswal *et al*., 2020). Numerous studies have indicated a link between polycystic ovary syndrome (PCOS) and a defect in the gene responsible for insulin function. Despite the variety of causes of this disease, it is important to treat it effectively. PCOS is one of the most important causes of infertility in women, but that does not mean that the patient cannot get pregnant. It can be treated by using drugs specifically designed to treat this disorder, such as anti-androgens. In some cases, the patient may need to undergo ovarian drilling surgery as a means of improving the condition (Teede *et al*., 2010). Polycystic ovary syndrome (PCOS) is characterized by the presence of small cysts filled with ovarian fluid. With scientific advancements, it has been discovered that PCOS can be detected through ultrasound examination, where a number of follicles are observed

in one or both ovaries with a radius ranging from 2-9 mm, or enlargement is seen in one or both ovaries reaching more than 10 cm (Dewailly, 2020). Studies have not reached a precise agreement on the causes of PCOS, and its nature remains not precisely known. There are many explanations and opinions about its occurrence (Serena L., 2013). Among the common causes mentioned in studies is a disturbance in the hormonal balance in the body, such as hyperandrogenism, represented by increased levels of testosterone and elevated levels of luteinizing hormone (LH). This disturbance leads to hirsutism, acne, and hereditary baldness (Gautam N., 2007). Physiological causes such as disorders and diseases of the pituitary gland (Serena, 2013), genetic factors that may play a role in the occurrence of polycystic ovary syndrome (Omair, 2013), and environmental factors such as pollution and some drugs may have an effect on polycystic ovaries (Nancy, 2006). Heredity also plays a role in the causes of the syndrome, as the genetic nature of patients is due to a gene of the dominant type, and its appearance is accompanied by the appearance of baldness in women with the syndrome, and the genetic cause is not discovered yet. It has also been shown that obesity and changes that occur in body composition are related to insulin resistance, which is one of the most important symptoms associated with the syndrome (Kristensen *et al*., 2010). The aim of this research is to reveal the relationship of single nucleotide polymorphisms (SNPs) of the rs10046 site in the aromatase gene CYP19A1 and some biochemical variables and their relationship to the occurrence of polycystic ovary syndrome (PCOS) in women.

MATERIALS AND METHODS

(90) samples were collected from women aged (16-45) years for this study from (1) November 2022 until (1) March 2023. The samples were divided into two groups, consisting of (60) patient samples and (30) healthy samples. The samples were collected from female consultants at Tikrit Teaching Hospital and female consultants in outpatient clinics by conducting the necessary analyses and ultrasound examinations to confirm whether or not they had the syndrome. The concentration of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), and Aromatase (CYP19A1) enzyme were measured. (5) ml of venous blood was drawn from each woman, whether or not she had polycystic ovary syndrome, during days (2-6) of the menstrual cycle. These samples were divided into two sections for analysis and study:

Section 1: Two milliliters (ml) of venous blood were placed in a tube containing EDTA (an anticoagulant). The sample was then placed in a cryotherapy unit for storage and subsequent use in DNA extraction and molecular studies.

Section 2: Three milliliters (ml) of blood were placed in silicone gel tubes. The samples were then centrifuged at 3500 rpm for 15 minutes to obtain serum. The serum was transferred to Eppendorf tubes and stored at -20°C. All relevant information regarding the samples was recorded and documented in preparation for use in the biochemical assays for the current study.

First: Measuring Luteinizing Hormone (LH) Concentration: The Monobind kit, which includes all the necessary steps for measuring LH concentration according to the manufacturer's instructions (Lentone *et al*., 1982), was used.

Second: Measuring Follicle Stimulating Hormone (FSH) Concentration: FSH was measured using the ELISA kit, as per the instructions of the manufacturer, Monobind (Vitt *et al*., 1998), as described in section one on measuring LH concentration.

Third: Measuring Aromatase (CYP19A1) Concentration: Aromatase (CYP19A1) concentration was measured using the Sunlong kit, following the instructions provided.

Molecular Study:

This study included the following:

DNA was extracted from blood samples of both women with and without polycystic ovary syndrome (PCOS) using a kit supplied by GENEAID. Genomic DNA was extracted to detect the CYP19A1 aromatase gene polymorphism at the rs10046 locus using Tetra-ARMS PCR. The four primers were designed according to the specifications outlined by Anderson *et al*., (1999) for this study, using a PCR-Premix kit supplied by the Korean company Macrogene.

Rs10046 G wild\A Mutant

Annealing 62 Product size for G allele: 228 Product size for A allele: 315

Product size of two outer primers: 485

Table 1: Shows the name and sequence of the prefixes used in the research

Primer Name	Primer sequence
IF46	CTACTGATGAGAAATGCTCCAGATTGGAA
IF46	GGAACACTAGAGAAGGTGGTCAGTAACT
OF46	GAAGGCCTATCCTTCTCAAAGCACA
OR46	GTGATGATGAAAGCCATCCTCGTTA

When the product of the PCR reaction for the purpose of detecting the CYP19A1 aromatase gene polymorphism was transferred onto an agarose gel at a concentration of 1% for 45 minutes and when it was imaged with a UV Transilluminator, where the rs10046 site was shown, it showed that the wild allele (G) appears at the (228) bp band, while the mutant allele (A) appears at the (315) bp band, as in the following figure:

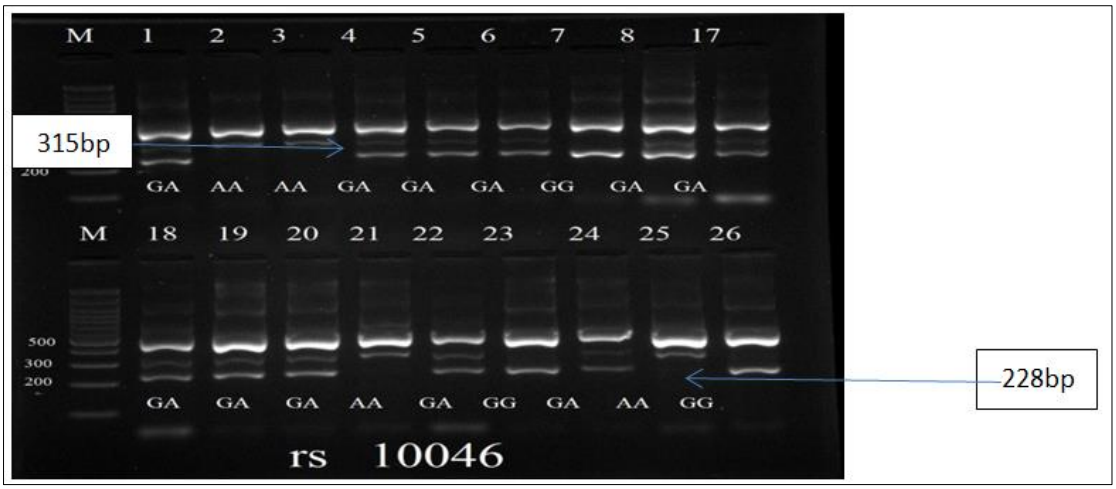

Figure showing the genotypes resulting from electrophoresis using T-ARMS PCR on a 1% agarose gel for the aromatase gene at the (rs10046) site and a volumetric indicator (DNA ladder 100bp Marker)

Statistical Analysis

After collecting genetic data on polycystic ovary syndrome patients and healthy individuals, I statistically analyzed it using Microsoft Excel and SPSS statistical analysis software to find the rates, percentages, and statistical tests necessary for this study.

LH/FSH Ratio

$$\text{LH/FSH} = \frac{\text{LH (mIU/mL)}}{\text{FSH (mIU/mL)}}$$

RESULTS AND DISCUSSION

The LH/FSH ratio analysis is an important analysis in PCOS studies because it is a direct functional indicator of hypothalamic-pituitary-ovarian axis disorder, and is often more sensitive than LH or FSH analysis alone. Its levels in normal women are: often ≈ 1, and in PCOS patients: often > 2. This ratio reflects increased pituitary LH secretion, ovulation disorder, and increased androgens. Table (2) shows the distribution of aromatase gene genotypes between patients with polycystic ovary syndrome (PCOS) and healthy individuals. No statistically significant differences were observed in genotype frequencies between the two groups ($\chi^2 = 0.115$, $p = 0.900$). Allele frequency analysis also revealed no statistically significant association between the R and G alleles and predisposition to PCOS ($\chi^2 = 0.0028$, $p = 0.969$). The calculated odds ratio for the G allele was 1.05 (95% CI: 0.61–1.79), indicating no significant genetic risk associated with this polymorphism. These results indicate that the studied polymorphism does not play a major role in the mechanism of polycystic ovary syndrome in the studied population. Previous studies have indicated similar results, showing that the contribution of CYP19A1 gene variants to the risk of developing polycystic ovary syndrome may be specific to a particular population or influenced by gene-environment interactions. Studies that evaluate phenotypes associated with abnormalities indicate a paradoxical function of estrogen in growth and differentiation in addition to steroid sex hormones (Di Nardo, 2021). The development of polycystic ovary syndrome has been observed in patients with reduced aromatase activity or aromatase deficiency due to the presence of rare mutations leading to loss of function (Mostafa et al., 2016). The lack of correlation may also reflect the multifactorial nature of polycystic ovary syndrome, where multiple genetic and environmental factors interact to influence disease development, and environmental factors such as pollution and certain medications may have an effect on polycystic ovaries (Nancy, 2006).

Table 2: Number of aromatase gene alleles and their frequency rates in polycystic ovary syndrome patients and healthy individuals

(95% CI)	OR	*P* Value	Control No (30)		Patients No (60)		Genotypes
			Freq. %	No.	Freq. %	No.	
0.115	1.7	0.9	20	6	20	12	RR
			50	15	46.67	28	GR
			30	9	33.33	20	GG
(95% CI)	**OR**	***P* Value**	**Freq.**	**No.**	**Freq.**	**No.**	**Alleles**
0.61 to 1.79	1 Ref.	0.969	45	27	43.33	52	R
	1.05		55	33	56.67	68	G

Analysis of Aromatase Gene Levels According to Genotype

Table (3) shows the average aromatase concentrations according to the genotype. It is noted that there is a clear increase in the average gene expression of the aromatase gene in the patient group compared to healthy individuals, especially in the RR genotype. It is also noted that the high standard deviation in the patient group (especially RR and GR) indicates a large biological variation between the cases, which is common in polycystic ovary syndrome as a result of the difference in disease severity and hormonal response. In the control group, the values were more homogeneous, which indicates the stability of gene expression in the normal physiological state.

Table 3: Average aromatase concentrations according to genotype

Genotype	Average healthy people ± SD	Average patients ± SD
RR	28.91b ± 4.65	34.63a ± 26.27
GR	30.56b ± 14.79	32.32a ± 27.44
GG	26.88b ± 4.33	31.97a ± 19.64

LH Hormone

Serum luteinizing hormone (LH) levels were compared between different genotypes (LL, GL, and GG) in both patients with polycystic ovary syndrome (PCOS) and a control group of healthy women. Table 4 shows no significant differences in LH levels between the three genotypes (LL, GL, and GG) in patients or healthy individuals. The observed differences are individual variations and not statistically significant. In PCOS patients, the mean LH levels were 9.32 ± 5.41, 17.26 ± 14.61, and 18.97 ± 15.90 for genotypes LL, GL, and GG, respectively. One-way analysis of variance (ANOVA) showed no statistically significant differences between the genotypes ($F = 1.88$, $p = 0.161$). Similarly, in the control group, the mean LH levels were 6.58 ± 2.63 (LL), 6.57 ± 2.04 (GL), and 7.60 ± 1.30 (GG), with no statistically significant differences ($F = 0.45$, $p = 0.642$). These results indicate that aromatase gene polymorphisms do not significantly affect LH levels in either polycystic ovary syndrome (PCOS) patients or healthy individuals, suggesting that LH dysfunction in PCOS is more influenced by pituitary and hypothalamic dysfunction, as well as environmental or metabolic factors, than by single gene polymorphisms. Furthermore, the wide variation observed within the genotype groups highlights the multifactorial nature of polycystic ovary syndrome, so studies on larger groups and multigene interaction analyses are recommended to elucidate the genetic mechanisms involved more deeply.

Table 4: Number of LH hormone gene alleles and their frequency rates in polycystic ovary syndrome patients and healthy individuals

(95% CI)	OR	*P* Value	Control No (30)		Patients No (60)		Genotypes
			Freq. %	No.	Freq. %	No.	
0.115	1.88	0.161	50	15	20	12	LL
			30	9	45	27	GL
			20	6	35	21	GG
(95% CI)	**OR**	***P* Value**	**Freq.**	**No.**	**Freq.**	**No.**	**Alleles**
0.61 to 1.79	1 Ref.	64.25	45	27	43.33	52	L
	0.45		55	33	56.67	68	G

Average LH Hormone Concentrations According to Genotype in Polycystic Ovary Syndrome Patients and Healthy Women

Table (5) shows the average concentrations of luteinizing hormone (LH) according to the different genotypes LL, GL, GG in both the polycystic ovary syndrome (PCOS) patient group and the healthy group. The results showed a significant increase in LH concentrations in the patients compared to the healthy group in all genotypes. The highest average was 18.97 in the patients with the GG genotype, while the lowest average was 6.57 in the healthy group with the GL genotype. No significant differences were observed between the genotypes in the healthy group, as all of them were within the normal level of LH. A high standard deviation was also observed in the GL and GG genotypes in the patients. This indicates a significant variation in the severity of hormonal imbalance between cases, which is common in polycystic ovary syndrome due to the varying degrees of hyperactivity of the hypothalamic axis in the brain. The results also suggest that the presence of the G allele in the GL and GG patterns may be associated with increased activity of the hormonal pathways regulating LH secretion or with increased ovarian sensitivity to it. This explains the greater increase in LH concentration in carriers of this allele compared to the LL pattern. This is consistent with several studies that have indicated that some genetic polymorphisms in genes regulating ovarian function or reproductive hormones may affect the severity of hormonal imbalance in polycystic ovary syndrome patients. Therefore, these results suggest a possible association between the studied genotype and the level of LH hormone imbalance in polycystic ovary syndrome, and that the G allele may represent a genetic risk factor associated with increased severity of hormonal imbalance.

Table 5: Average LH concentrations by genotype in polycystic ovary syndrome patients and healthy women

Genotype	Average healthy people ± SD	Average patients ± SD
LL	6.58c ± 2.63	9.32b ± 5.41
GL	6.57c ± 2.04	17.26a ± 14.61
GG	7.60c ± 1.30	18.97a ± 15.90

FSH Hormone

The results in Table (6) show that there are no statistically significant differences between the genotypes, but there is a biological trend towards a decrease in FSH with the G allele, which gives the impression that the G allele does not directly affect the level of FSH, but may contribute to modifying the hormonal response in the presence of the disease, which indicates that the gene's effect is modulatory and not a direct cause, and this is consistent with the multifactorial nature of polycystic ovary syndrome. No statistically significant differences were observed in the frequencies of the genotypes between the two groups (χ^2 = 1 Ref., p = 0.51). Allele frequency analysis also revealed no statistically significant association between the F and G alleles and predisposition to polycystic ovary syndrome (χ^2 = 2.68, p = 0.086), with the calculated odds ratio for the G allele being 1 Ref. (95% CI: 0.61–1.79).

Table 6: Number of alleles of the FSH hormone gene and their frequency rates in patients with polycystic ovary syndrome and healthy individuals

(95% CI)	OR	*P* Value	Control No (30)		Patients No (60)		Genotypes
			Freq. %	No.	Freq. %	No.	
0.68	1 Ref.	0.51	50	15	20	12	FF
			20	6	46.67	28	GF
			30	9	33.33	20	GG
(95% CI)	**OR**	***P* Value**	**Freq.**	**No.**	**Freq.**	**No.**	**Alleles**
0.61 to 1.79	1 Ref.	0.086	45	27	43.33	52	F
	2.68		55	33	56.67	68	G

Average FSH Concentrations by Genotype

Table (7) shows a relative increase in FSH levels among carriers of the G allele, with a gradual decrease from FF to GG. High variability is also observed within the patient group, a common pattern in PCOS resulting from a disturbance in the hypothalamic-pituitary-adrenal axis. In contrast, the variability was lower in healthy individuals, reflecting hormonal stability.

Table 7: Average FSH concentrations according to genotype

Genotype	Average healthy people ± SD	Average patients ± SD
FF	7.39 ± 1.46	6.41 ± 3.59
GF	6.20 ± 1.94	9.42 ± 7.83
GG	5.01 ± 2.26	8.59 ± 7.80

LH/FSH Ratio

Table (8) shows the calculation of the LH/FSH ratio to assess hormonal imbalance across aromatase gene genotypes in patients with polycystic ovary syndrome. The LH/FSH ratio showed a gradual increase from AA genotype (2.51 ± 2.93) to GA genotype (3.33 ± 2.81) and then to GG genotype (3.90 ± 4.94): AA → GA → GG. In contrast, the control group showed ratios within physiological limits, with mean values of 0.91 ± 0.35, 1.18 ± 0.50, and 1.49 ± 0.46 for genotypes AA, GA, and GG respectively. These results indicate a tendency for hormonal imbalance in patients with polycystic ovary syndrome due to altered aromatase activity and increased ovulation disturbance. This is consistent with increased LH secretion and decreased conversion to estrogen, which is genotype-dependent. The current results show a gradual increase in the LH/FSH ratio in G allele carriers of polycystic ovary syndrome, indicating a possible role for aromatase gene polymorphisms in modifying gonadotropin imbalance. There is also variability and a rise in standard deviation values in patients, while all values were within the normal physiological range in healthy individuals, with only a slight increase in the G allele without hormonal disturbance. This indicates that the gene's effect is modulatory and not a direct cause. Thus, this study confirms that the gene has no direct effect on LH or FSH individually, but there is a clear effect on the LH/FSH ratio. While this effect was not evident in healthy individuals, indicating that genetic variation may only affect hormonal imbalance in the presence of an underlying ovarian dysfunction, these results support the multifactorial nature of polycystic ovary syndrome, which includes both genetic predisposition and hormonal changes. This is consistent with what concluded (Gautam N, 2007).

Table 8: Average LH/FSH ratio by genotype

Genotype	Average patients ± SD	Average healthy people ± SD
AA	2.51 ± 2.93	0.91 ± 0.35
GA	3.33 ± 2.81	1.18 ± 0.50
GG	3.90 ± 4.94	1.49± 0.46

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