

## Original Article

# Association of polycystic ovarian syndrome with inflammatory single nucleotide polymorphism for IL-1 & IL-6 genes: A case-control study

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**Background & objectives:** Persistent mild inflammation is considered as a main contributor to the altered genesis of polycystic ovary syndrome (PCOS), with numerous studies reporting elevated serum levels of inflammatory markers. This inflammatory state may be attributed to genetic variants, particularly single nucleotide polymorphisms (SNP), that alter cytokine regulation. This study investigated the association of PCOS and inflammatory SNPs including interleukin (IL) such as *IL-1β* rs1143634, *IL-1β* rs16944, *IL-6* rs1800795, *IL-6* rs1800797, *IL-6* rs1800796, *IL-1RN*; and tumour necrosis factor-alpha (TNF-α).

**Methods:** A total of 250 women volunteered for the study; of which 100 were diagnosed with PCOS and 150 were healthy controls. Serum levels of IL-6, IL-1β, and TNF-α were measured using enzyme-linked immunosorbent assay (ELISA). Genotyping was analysed using polymerase chain reaction (PCR), PCR-restriction fragment length polymorphism (PCR-RFLP), or real-time PCR (RT-PCR). Genotype distributions amid groups were compared using the Chi-square test.

**Results:** Women with PCOS exhibited elevated serum levels of IL-1β than those of healthy controls which was considerably significant ( $P < 0.001$ ). The heterozygous genotypes of *IL-1RN* and *IL-6* rs1800796 were seen more frequently in the control group ( $P = 0.02$ ), suggesting a potential inverse association.

**Interpretation & conclusions:** SNPs in *IL-1* and *IL-6* genes may influence susceptibility to PCOS and could confer a protective role in women of South Asian Indian origin.

**Key words** Cytokines - genetic - interleukins - ovary - polymorphism

Polycystic ovarian syndrome (PCOS) is a common continual endocrine disorder afflicting woman in the fertile age group<sup>1</sup>. The global burden of disease (GBD) study, done from 1999 to 2010, has estimated

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an approximate of 116 million women worldwide to be affected with PCOS<sup>2</sup>. Globally, around 1.55 million incident cases have been reported over the past decade, which reflects a recent rise of 4.46 per cent of PCOS cases<sup>3</sup>.

In addition to the typical clinical symptoms of altered ovulatory cycles, excess androgen levels and multiple ovarian cysts, these women are vulnerable to several complications such as unstable blood sugar levels, elevations in blood pressure, myocardial abnormalities, barrenness and even neoplasms of reproductive organs<sup>4</sup>. The increased occurrence of cardiovascular and metabolic complications among PCOS women has prompted some scientists to also name this disease as a 'metabolic reproductive syndrome'<sup>5</sup>. Due to its increasing incidence and prevalence as well as its related complications, studying factors that influence the predisposition to PCOS is warranted. The exact occurrence of PCOS still remains unsure; nevertheless, different proposed mechanisms that could possibly lead to this syndrome include altered steroid regulation, stress, continual mild inflammation, distorted insulin sensitivity, a slack in metabolism, genetic linkages and obvious wrong lifestyle choices<sup>1</sup>. It is interesting to note that pro-inflammatory cytokines are elevated in serum samples of PCOS women. It is believed these cytokines are released from adipocytes and granulosa cells of polycystic ovaries. It has been reported that PCOS granulosa cells express elevated transcripts that encode these cytokines and immune cell markers<sup>6</sup>.

Elevated serum levels of inflammatory cytokines observed in PCOS could be a consequence of functional alterations caused by single nucleotide polymorphisms (SNPs) in inflammatory cytokines genes<sup>7</sup>. One such gene is interleukin-6 (*IL-6*), an inflammatory cytokine that functions in inflammation as well as immune regulation. *IL-6* accelerates both B-cell differentiation and T-cell proliferation<sup>8</sup>. Another possible candidate gene, interleukin-1 beta (*IL-1β*) gene plays a vivid role in reproductive physiology and has been implicated as an essential regulatory factor in ovulation, fertilization, and embryo implantation<sup>9</sup>. Additionally, tumour necrosis factor-alpha (*TNF-α*) is a proinflammatory cytokine formed by various immune cells such as antigen stimulated T cells, lymphocytes and NK cells<sup>10</sup>. Reports have indicated that there is a rise of these inflammatory markers in women with PCOS<sup>11-13</sup>. Variants in its corresponding genes have also been found to be associated with PCOS<sup>14,15</sup>.

The present study investigated the association between seven functionally most relevant SNPs in

inflammatory genes and PCOS among South Asian Indians. Also, since SNPs can influence the function of these genes either qualitatively or quantitatively, studying this association would be beneficial. Hence, the aim was to study the cytokine gene polymorphisms *IL-1β* +3954 C/T (rs1143634), *IL-1β* -511 T/C (rs16944), *IL-6* -174 G/C (rs1800795), *IL-6* -597G/A (rs1800797), *IL-6* -634 C/G (rs1800796) *TNF-α* -1031 T/C (rs1799964) and *IL-1* RN among Indian women with PCOS.

## Materials & Methods

This study was conducted as a comparative cross-sectional design by the department of Physiology, Sri Ramachandra Institute of Medical Sciences, Chennai, Tamil Nadu, India over a time span of four years from November 2018 to February 2023. Ethics approval was obtained from the Institutional Ethics Committee prior to the initiation of the study.

*Study population:* A total of 250 participants between the ages of 18 and 30 yr were enrolled, of which 100 women were diagnosed cases of PCOS and 150 were healthy women volunteers. For a 95 per cent confidence and 80 per cent power, the required sample size was 150 (75 cases, 75 controls). Participants with PCOS were grouped based on Rotterdam criteria satisfying no less than 2 of the following features: oligomenorrhoea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism or polycystic ovaries as seen on ultrasound. The healthy women included in the study confirmed regular menstrual cycles with no features of PCOS. Participants with a recent history of fever/infection within the past four wk, severe systemic illness, inherited adrenal hyperplasia, Cushing syndrome, on medications known to alter insulin hemodynamics, on oral contraceptives or anti-obesity drugs, on any anti-inflammatory therapy, any form of arthritis or pregnant/nursing mothers were excluded from the study.

Details such as age, menstrual history, stress symptoms, diet, physical activity, family history of PCOS and medical and drug history were obtained using a questionnaire. Height (cm) and weight (kg) were measured and documented. Body mass index (BMI) was then calculated by dividing the weight (kg) by the squared height (m).

*Assessment of serum inflammatory levels:* Serum inflammatory levels were quantified using enzyme linked immunosorbent assay (ELISA). The kits used for assessment of serum *IL-6*, *IL-1β* and *TNF-α* were two each of human *IL-6* ELISA kit (96 wells), human

**Table I.** Characteristics of the study population

Variable	Polycystic ovarian syndrome S, n=100	Healthy women, n=150	P value
Age (18-35 yr)	23.6±3.9	22.4±3.9	0.12
Height (cm)	158.0±7.83	158.5±6.7	0.4
Weight (kg)	66.0±13.4	58.4±13.1	<0.001
BMI (kg/m <sup>2</sup> )	26.5±4.8	23.2±4.7	<0.001 (OR:3.97, CI: 2.08 - 7.79)
Family history of PCOS			
Present	17 (17%)	13 (8.7%)	0.01 (OR: 3.21, CI: 1.21 - 8.52)
Serum inflammatory levels			
IL-6 (pg/mL)*	1.10±2.64	0.85±2.03	0.3
IL-1 $\beta$ (pg/mL)*	20.39±17.52	8.62±10.95	<0.001
TNF- $\alpha$ (pg/mL)*	11.12±20.37	10.80±21.57	0.13

\*Normal range-IL-6:0 -16.4 pg/mL, IL-1 $\beta$ :0 -6.5 pg/mL, TNF- $\alpha$  : 0 -8 pg/mL

IL-1 beta ELISA kit (96 wells) and human TNF-alpha ELISA kit (96 wells), respectively. The assays were performed as per the manufacturer's instructions. Using calibration controls, a standard curve was obtained with which the results were interpreted.

**Genotyping:** Genomic deoxyribonucleic acid (DNA) was isolated from leucocytes of peripheral blood using the blood DNA isolation kit (QIAGEN, Hilden, Germany). Supplementary table shows the primary information on the genotyping assays for all the polymorphisms studied. Five polymorphisms, *IL-1 $\beta$*  +3954 C/T (rs1143634), *IL-1 $\beta$*  -511 T/C (rs16944), *IL-6* -597G/A (rs1800797), *IL-6* -634 C/G (rs1800796) and *TNF- $\alpha$*  -1031 T/C (rs1799964), were analyzed through polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP). All the reactions were performed in a final volume of 20  $\mu$ L containing 25 pmol of each primer, 2 mM of each dNTP, 1.5 mM MgCl<sub>2</sub>, 1X Taq DNA polymerase buffer and 0.5 U of Taq DNA polymerase. The amplicons digested with appropriate restriction enzymes (New England Biolabs) were electrophoresed on a 4 per cent agarose gel and visualized under a ultraviolet transilluminator. Restricted product sizes were observed to assign genotypes.

The *IL-1* RN variable number of tandem repeat polymorphism (VNTR) was assessed by running the PCR product on a 4 per cent agarose gel. The alleles were identified based on the base pair size as mentioned in supplementary table. For *IL6*-174 G>C (rs1800795), RFLP was not suitable as the base pair size difference between the alleles was small, which could not be reliably resolved on agarose gel. Hence, real-time PCR, a more robust and sensitive method for SNP genotyping, was employed, using TaqMan custom-

designed SNP genotyping assay (Applied Biosystems) with the ABI 7500 fast real-time PCR system.

**Statistical analysis:** For each polymorphism, compliance of genotype frequencies with the Hardy-Weinberg equilibrium (HWE)<sup>16</sup> was measured using a Chi square test, with the level of significance set to  $P<0.05$ , using a web-tool ( $\chi^2$  test) HWE calculator. For an evaluation of the genotype frequencies for each SNP between the groups, Chi-square test and odds ratio (OR) at 95 per cent confidence interval (CI) were performed with  $P<0.05$  as statistically considerable. The SNP STAT web tool software (<https://www.snpstats.net/start.htm>) was used to ascertain risk based on the combined genotypes of all the polymorphisms studied.

## Results

Two hundred and fifty women participated in this study with 100 diagnosed with PCOS. A comparison of age, weight, height, body mass index (BMI) and family history were done as shown in table I. The odds ratio of PCOS women having above-normal BMI was 3.97. Odds ratio for PCOS women to have a positive family history of PCOS was 3.21. Serum levels of IL-1, IL-6, and TNF- $\alpha$  between the diseased and controls are also compared in table I.

**HWE:** HWE was calculated for PCOS and healthy women under each genetic polymorphism. Among the PCOS group, HWE was consistent for the polymorphisms *IL-1 $\beta$*  (+3954 C/T) rs1143634, *IL1 $\beta$*  (-511 T/C) rs16944, *IL-6* (-174 G/C) rs1800795, *IL-6* (-597G/A) rs1800797 and *TNF- $\alpha$*  (-1031 T/C) rs1799964. While among the healthy women, the genotype frequencies for *IL-1 $\beta$*  (+3954 C/T) rs1143634,

**Table II.** Comparison of genotype distribution between PCOS and healthy women

Genotypes	PCOS (n=100)	Healthy women (n=150)	OR	95% CI	P value
<i>IL-1β</i> rs1143634 (+3954 C/T)					
CC	85	137		Ref	
CT	13	13	1.6	0.7 - 3.6	0.25
TT	2	0	0.1	0.01 - 2.6	0.18
Dominant model (CC vs. CT+TT)	15	13	1.8	0.8 - 4.0	0.12
Recessive model (TT vs. CC+CT)	2	0	8.0	0.3 - 169.5	0.18
<i>IL-1β</i> rs16944 (-511 T/C)					
TT	38	64		Ref	
TC	52	72	0.7	0.4 to 1.3	0.33
CC	10	24	0.7	0.3 to 1.6	0.40
Dominant model (TT vs. TC+CC)	62	96	1.0	0.6 to 1.8	0.74
Recessive model (CC vs. TT+TC)	10	24	0.6	0.2 to 1.3	0.25
<i>IL-6</i> rs1800795 (-174 G/C)					
CC	71	104		Ref	
CG	24	41	0.8	0.4 to 1.5	0.60
GG	5	5	1.4	0.4 to 5.2	0.56
Dominant model (CC vs. CG+GG)	29	46	1.0	0.6 to 1.8	0.83
Recessive model (GG vs. CC+CG)	5	5	1.4	0.4 to 5.2	0.56
<i>IL-6</i> rs1800797 (-597G/A)					
GG	86	129		Ref	
GA	11	16	1.0	0.4 to 2.3	0.94
AA	3	5	0.9	0.2 to 3.8	0.88
Dominant model (GG vs. GA+AA)	14	21	1.0	0.4 to 2.0	1.00
Recessive model (AA vs. GG+GA)	3	5	0.9	0.2 to 3.8	0.88
<i>IL-6</i> rs1800796 (-634 C/G)					
CC	32	30		Ref	
CG	34	70	0.4	0.2 to 0.8	0.02*
GG	34	50	0.6	0.3 to 1.2	0.18
Dominant model (CC vs. CG+GG)	68	120	0.4	0.2 to 0.8	0.01*
Recessive model (GG vs. CC+CG)	34	50	0.6	0.3 to 1.2	0.18
<i>TNF-α</i> rs1799964 (-1031 T/C)					
TT	60	100		Ref	
TC	29	33	1.4	0.8 to 2.6	0.20
CC	11	17	1.0	0.4 to 2.4	0.86
Dominant model (TT vs. TC+CC)	40	50	1.3	0.7 to 2.2	0.28
Recessive model (CC vs. TT+TC)	11	17	1.0	0.4 to 2.4	0.85
<i>IL-1</i> RN					
RN-1	42	55		Ref	
RN-2	2	4	0.6	0.1 to 3.7	0.63
RN-3	3	0	9.1	0.46 to 181.7	0.15
RN-4	19	24	1.0	0.50 to 2.1	0.92
RN-5	0	1	0.4	0.02 to 10.9	0.61
RN- 1,2	23	40	0.7	0.40 to 1.4	0.39
RN- 1,3	1	14	0.1	0.01 to 0.7	0.02*
RN- 1,4	1	2	0.6	0.06 to 7.4	0.73
RN-2,4	0	1	0.4	0.02 to 10.9	0.61
RN-3,4	9	8	1.4	0.52 to 4.1	0.46
RN-4,5	0	1	0.4	0.02 to 10.9	0.61

*IL-6* (-634 C/G) rs1800796, *IL-6*(-174 G/C) rs1800795 and *IL-1* RN followed the HWE.

*Genotype frequencies of cytokine gene polymorphisms:*

The genotype frequencies of each cytokine genotype polymorphism along with dominant and recessive models are depicted in Table II. For *IL-6* rs1800796 (-634 C/G) and *IL-1* RN polymorphisms, the frequency of the CG genotype and RN-1,3 among PCOS women was 34 and 1, respectively while that among healthy women was 70 and 14 respectively ( $P$ -value=0.02). Moreover, in the dominant model (CC vs CG+GG) frequency of the CG+GG genotype was observed to be 68 among women with PCOS and 120 among healthy volunteers (OR = 0.04,  $P$  = 0.01). For the remaining SNPs,  $P$ -value was found to be more than 0.05. A multi-SNP analysis was performed to determine if there was a combined association that could modify the risk and  $P$ -value obtained in all the combinations were more than 0.05 (data not shown).

### Discussion

PCOS is considered as an inflammatory condition with current data suggesting that persistent mild inflammation impacts the progress of its clinical features<sup>17</sup>. The results indicated that women with PCOS had a significantly higher inflammatory state of IL-1 $\beta$  serum levels compared to healthy women. Moreover, the *IL-1* RN heterozygous genotype of 1 and 3 repeats and *IL-6* rs1800796 (-634 C/G) heterozygous CG genotype had an inverse association with the development of PCOS. The remaining SNPs did not show any association.

This study has its strengths and limitations. It uniquely combines the analysis of serum levels of inflammatory markers with their corresponding genetic polymorphisms, enhancing the reliability and validity of the findings. Some of the SNPs examined for their association with PCOS in a relatively large sample size were not previously explored in similar studies, Functional assays were beyond the scope of this work, but our findings provide a necessary foundation for future mechanistic studies. The sample size, though modest, was sufficient to detect allele-level associations for common variants and comparable to prior studies in this field. Minor deviations from Hardy–Weinberg equilibrium likely reflect random variation or subtle population substructure rather than genotyping errors, as quality controls were rigorously applied. Although the study was conducted at a single center, the uniform diagnostic criteria and homogeneity of the cohort

enhance internal validity. Finally, multiple comparison corrections were not applied in this exploratory design to avoid overlooking potential associations, but the observed trends remain consistent with existing literature, supporting their relevance.

In the present study, the serum IL-1 $\beta$  was found to be significantly higher in women with PCOS. This finding is similar to a study done in 2023, where IL-1 was significantly elevated in women with PCOS<sup>18</sup>. However, the selected polymorphisms of IL-1 $\beta$  gene (rs1143634 and rs16944) did not show any association with PCOS. Considering that higher serum IL-1 $\beta$  levels in PCOS was observed with non-association of this SNP, it could be that either other IL-1 $\beta$  SNPs are influencing this trend, or a non-genetic mechanism caused this observation.

Higher frequency of IL- RN 1, 3 genotype in healthy women could possibly mean that RN-1, 3 is involved in reducing the risk of developing PCOS as IL-1 is known to influence healthy ovarian function, fertilization and implantation<sup>19</sup>. This finding goes parallel to a review study done in 2018, where IL-1RA was believed to minimize inflammatory response<sup>20</sup>. The association of this VNTR with PCOS has been studied in other populations as well. Comparable findings were obtained by scientists where IL-RN did not contribute to PCOS risk<sup>21,22</sup>.

Of the three polymorphisms of *IL-6* analyzed, *IL-6* rs1800795 (-174C/G) and *IL-6* rs1800797 (-597G/A) did not show an association with PCOS. This finding is similar to a meta-analysis published in 2015<sup>23</sup>, where no association of rs1800795 with PCOS was found but rs1800796 showed inverse association with PCOS in this study where the CG genotypes were more frequent in healthy women. The dominant model of this latter SNP also showed an inverse association. Both these results suggest that this SNP could also be involved in the reduced susceptibility for PCOS. Corresponding serum levels did not show a statistical difference between the two groups. The possible reason for this could be the presence of many other factors that could disguise or overrule the gene's potential effect on IL-6 serum levels. Some of these factors could be other gene interactions, complex regulatory pathways and environmental influences. We could not find any published association data of rs1800796 SNP with PCOS till date.

The effect of considering multiple SNPs in the risk assessment was also assessed. The rationale for this analysis was based on the fact that it is logical

to contemplate that inflammatory genes collectively modulate the inflammatory response<sup>24</sup>. Hence, multiple SNP analysis was an acceptable means to assess this. The analysis did not reveal any association which could imply that the selected frequent SNPs are likely to describe only a part of the variation leading to PCOS. Since this study focused only on common variants, exceedingly influential atypical variants in these genes need to be studied to find their role in PCOS.

In conclusion, these findings suggest a protective role of *IL-1* RN 1, 3 and *IL-6* (-634 C/G) rs1800796 genotype against PCOS by modulating folliculogenesis and implantation and therefore could have a role in diminishing the risk for PCOS among women of South Asian Indian origin. This information can now be used to design future experimental studies to elucidate the mechanisms. For instance, conducting prospective cohort studies would be valuable to establish temporality and causality between inflammatory markers and its corresponding gene polymorphisms with the development and progression of PCOS. Also, mechanistic studies, such as *in vitro* experiments using organoid models and animal models, can help uncover the specific pathways involved and provide a deeper understanding of the genetic mechanisms driving PCOS development. Intervention studies can evaluate the effectiveness of targeted interventions by complimentary therapy like an anti-inflammatory diet to modulate inflammatory markers and cytokine gene expression in PCOS women.

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