

Role of Leptin Gene Variants in Oxidative Stress–Mediated Pathogenesis of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine–metabolic disorder affecting women of reproductive age. Genetic, hormonal, and oxidative stress mechanisms underlie its heterogeneous presentation. Leptin, encoded by the LEP gene, plays a pivotal role in regulating energy balance, inflammation, and reproduction. Polymorphisms in the LEP gene, particularly the promoter variant –2548G/A (rs7799039) modulate leptin levels and metabolic responses. Recent evidence also implicates oxidative stress, characterised by excessive reactive oxygen species (ROS) and impaired antioxidant defence, in PCOS pathogenesis. This review summarises current knowledge on the molecular interplay between leptin gene polymorphisms and oxidative stress in PCOS, drawing insights from both global and Indian populations. We highlight genetic mechanisms, biomarker correlations, and potential therapeutic implications.

Keywords: Leptin, LEP gene, polymorphism, oxidative stress, PCOS, insulin resistance, Inflammation

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a widespread endocrine disorder in fertile women. Though most of the time its onset starts at the adolescent stage, the level and pattern of symptoms can change throughout the life of a woman. PCOS is a disorder of hormones, abnormal menstrual cycles, surplus production of androgens, and the existence of several small cysts in the ovaries. Ovulation is mostly related to menstrual irregularities, which considerably decrease the chances of conception, and as such, PCOS is one of the major causes of infertility in women. The condition is long-term and incurable, but the manifestations can be controlled successfully using lifestyle changes, pharmacological treatment, and assisted reproductive therapy. Though the pathogenesis is still not well understood, an increased likelihood has been noted among women having a family history of PCOS or type 2 diabetes mellitus.[1].PCOS is one of the most common endocrine diseases in reproductive women all over the world with a prevalence rate that is estimated to be between 8 and 20 percent depending on the population and criteria adopted to diagnose the condition. Pathophysiology of PCOS has a complex and multifactorial nature and it is a combination of genetic predisposition, environmental factors, hormonal imbalances, and metabolic imbalances. The imbalance of adipokines and the augmented oxidative stress have been identified in recent years as the key factors that connect the metabolic malfunction to reproductive abnormalities in the

involved women.PCOS can present with a wide range of clinical symptoms, including manifest themselves in different ways and may vary over time; in many cases, the trigger cannot be identified. The typical symptoms are heavy, prolonged, irregular or absent menstrual cycles, infertility, acne and greasy skin, excessive development of facial or body hair (hirsutism), male pattern baldness or loss of scalp hair, as well as weight gain, particularly of the abdominal or waist area. Besides reproductive complications, women with PCOS are prone to various long-term health disorders, such as type 2 diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease, and endometrial cancer. In addition to its physical health effects, PCOS can also have a significant psychological effect and add to anxiety, depression, and low self-esteem. The results of obesity, infertility and unwanted hair growth can cause social stigma, which can influence individual relationships, their performance at work, and involvement in social and communal life in general.

PREVALENCE OF PCOS

PCOS in Indian Patients: Prevalence.

Research evaluating the PCOS prevalence in India reveals that it has a great disparity based on the population, diagnosis criterion (NIH, Rotterdam, AES), age group, and area. Using a wider range of criteria such as Rotterdam or AES, which gives a prevalence of approximately 11.3% in Indian women of reproductive age, systematic reviews and meta-analyses approximate

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a pooled prevalence of about 11.3% in Indian women of reproductive age, although the NIH criteria usually estimate a lower prevalence (~5.8%). [3].

Reported prevalence differences between Indian studies conducted on individuals varied between as low as ~3.7% (Lucknow) and as high as ~22.5% (Mumbai) which suggests that there are considerable regional and methodological variations [4]. A more recent study in the Delhi-NCR area showed a significantly high prevalence of 17.4% which is above most pooled estimates perhaps due to the urban lifestyle, obesity, and metabolic risk features. In general, prevalence in Indians is generally between about ~8-12 per cent, but certain community surveys are even higher, emphasising the issue of heterogeneity in screening and diagnostics.[5].

Globa(Foreign) Prevalence of PCOS:

According to international systematic reviews, PCOS has an incidence of approximately 9-12 percent among women with reproductive age around the world based on the criteria of diagnosis. For example, a comprehensive meta-analysis estimated a global pooled prevalence of ~9.2%, with 5.5% by NIH, ~11.5% by Rotterdam, and ~7.1% by AES criteria. Other large reviews had estimated the global prevalence of approximately 12.1% by Rotterdam criteria with geographical variation (greater in Eastern Mediterranean and South-East Asian regions). These trends are ethnic, lifestyle and diagnostic country-cultural influences [3].

LEPTIN GENE: STRUCTURE, FUNCTION, AND REGULATION

The leptin gene (LEP) is one of the key factors in energy balance, metabolism and reproductive physiology. Leptin has been discussed as an important molecular interconnection between the adipose tissue, central nervous system and peripheral metabolic organs since its discovery in 1994. Leptin synthesis, signalling, or regulation are changes that cause various metabolic and endocrine condition such as obesity, insulin resistance, and PCOS. It is thus very important to understand how the leptin gene can be regulated, its structure and its functioning in order to explain the role of this gene in normal physiology and disease conditions [6].

Structure of the Leptin Gene

LEP gene is within chromosome 7q31.3 and covers a region of about 16 kilobases of genomic DNA. The gene consists of three exons and two introns; however, only exons 2 and 3 are translated to form the leptin protein. Exon 1 is non-coding and it has regulatory elements that deal with the initiation of transcription. The promoter area that is located upstream of the coding sequence contains several binding sites of hormonal, nutritional and metabolic responsive transcription factors.

The LEP gene produces a protein of 167 amino acids, which is the pre-pro-lep-protein. The mature biologically active leptin protein is 146 amino acids (146 amino acids), after removal of a 21-amino acid signal peptide in the course of post-translational processing.

Leptin is a long-chain helical cytokine that is similar to other cytokines like interleukin-6. The importance of this structural feature is that it interacts with the leptin receptor (LEPR), which belongs to the class I cytokine receptor family. A number of single-nucleotide polymorphisms (SNPs) have been detected in the LEP gene. One of them, G2548A (rs7799039) polymorphism in the promoter region, has attracted significant interest because it has the potential to affect the transcription of leptin genes and the levels of leptin in the body, the insulin type present in the body, and the leptin resistance levels in the body. These genetic variations can lead to ethnic variations in leptin expression and predisposition to metabolic diseases.

Function of Leptin

The main production and secretion sites of leptin are the white adipose tissue, and the level circulating in the blood will indicate the volume and the activity of the fat deposits. Leptin functions as a satiety hormone and it transmits the information about the energy stores in peripheral tissues to the hypothalamus in the brain. Leptin attaches to the leptin receptors in the arcuate nucleus and suppresses orexigenic receptors of the arcuate nucleus, including neuropeptide Y (NPY) and agouti-related peptide (AgRP), and activates anorexigenic receptors of the arcuate nucleus, including pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART). These processes result in the leptin decreasing appetite and increasing energy usage. In addition to controlling appetite, leptin is also important in metabolism of lipids and glucose. It increases the insulin sensitivity by regulating the level of glucose production in the liver and also by increasing the uptake of glucose in the peripheral tissues. Leptin also controls fatty acid oxidation and prevents the ectopic lipid deposition, thus safeguarding against lipotoxicity. Leptin is also significant in reproductive physiology. Normal reproductive processes require adequate levels of leptin to initiate and sustain normal reproductive functions since leptin is evidence of adequate energy for reproductive processes to occur. Among females, leptin has an impact on gonadotropin-releasing hormone (GnRH) secretions and ovarian steroidogenesis. Leptin dysregulation has been related to disorders affecting reproductive functions like PCOS where hyperleptinemia and leptin resistance could help mediate anovulation and hormonal imbalance. Moreover, leptin is an immunomodulatory and pro-inflammatory cytokine. It enhances macrophage, T cells/lymphocytes, and natural killer cell activation, which connects the nutritional status to immune competence. The persistent increase of leptin level as in the case of obesity is the cause of low-grade systemic inflammation which represents the feature of metabolic syndrome and PCOS.

Regulation of Leptin Gene Expression

There is an intricate balance and interaction between nutritional, hormonal, and neural factors and gene leptin expression. The adipose tissue mass is the most

significant factor that influences the concentration of leptins in the blood; persons who have a high body mass tend to have high leptin concentration. Nevertheless, high levels of leptin will not always result in decreased appetite because of the resistance to leptin especially in obesity. LEP is highly related to nutritional condition. Feeding and overnutrition stimulate leptin synthesis, and fasting and caloric restriction cause a rapid decrease in the leptin level, regardless of the changes in the fat mass. This adaptation is useful in saving energy during times of food starvation. There are several hormones that regulate transcription of the leptin gene. Insulin is a strong inducer of leptin expression which accounts for the increase in leptin during postprandial. Leptin synthesis is also facilitated by glucocorticoids, whereas leptin production is inhibited by catecholamines through β -adrenergic stimulation. The leptin expression is increased by sex hormones especially oestrogen thus explaining the elevated leptin concentrations in females compared to males at the same percentage of body fat. Genetically, transcription factor binding and gene expression can be changed under the influence of polymorphisms in the LEP promoter region. G2548A polymorphism was linked to the differences in leptin levels, body mass index, insulin resistance, and predisposition to metabolic disorders among populations. These genetic factors could be one of the reasons for inter-individual variability in leptin control and risk of illness. Stress factors such as environment and oxidation also affect the expression of leptin. Adiposity, inflammation, and dysfunction of the metabolic process are all linked in a feedback mechanism that can be stimulated by oxidative stress and pro-inflammatory cytokines. Such interaction is especially applicable in conditions such as PCOS, in which oxidative stress and persistent inflammation are accompanied by changes in leptin signalling. [7]. The LEP is a very essential controller of energy homeostasis, metabolism, reproduction and the immune system. Its well-organised genomic structure, cytokine-like protein product, and highly-regulated mechanisms have shown its relevance in physiology. Interference with the expression of leptin genes or signalling (genetic polymorphisms, hormonal imbalance, or environmental factors) may cause metabolic and reproductive diseases. The whole picture of the leptin gene structure, functioning, and control can offer good information regarding the pathophysiology of obesity, insulin resistance, and PCOS, and it can be used in the future to direct therapeutic approaches that target the leptin-related pathways.

COMMON LEPTIN GENE POLYMORPHISMS

Out of the LEP polymorphisms, the most widely examined polymorphism is -2548G/A (rs7799039), which is a promoter variant. This SNP influences transcription in the LEP gene resulting in increased serum leptin levels in A-allele carriers. Leptin and leptin receptor gene polymorphism have been widely studied with respect to their possible contribution to obesity and other associated metabolic characteristics, but with little evidence on the Asian population. Fan and Say

compared the common variants of the leptin gene (LEP A19 G and G2548A) and the leptin receptor gene (LEPR K109R and Q223R) to plasma leptin levels and obesity-related phenotype in a cohort of Malaysian multi-ethnic suburbs. Though none of the single polymorphisms was discovered to have a strong correlation with the presence of obesity, ethnic differences were significantly found in the genotype and allele distributions especially in the LEPR polymorphisms, and this is an indication of population-specific genetic backgrounds. It is worth mentioning that LEPR K109R and Q223R polymorphisms were linked to changes in blood pressure and fat distribution, with wild-type polymorphism consumers having a higher level of adiposity indices and plasma leptin concentrations, indicating changes in leptin signalling and not leptin deficiency. Notably, simultaneous examination showed that LEP and LEPR polymorphisms acted synergistically with those who were homozygous for all four showing much higher subcutaneous fat and circulating leptin levels. The results are consistent with the fact that cumulative genetic interactions in the leptin signalling pathway, but not individual genes, cause obesity. Li et al. [8] have found that the LEP G2548A polymorphism was more common in Caucasians compared to African Americans in people with average body weight. Conversely, the prevalence of the A allele was more common in the Asian population, especially those of Malays / Peninsular Bumiputras, Chinese and Indians. Other studies have failed to establish a notable relationship between this polymorphism and obesity such as a study carried out on the Tunisian [9], Pacific Islanders [10], Spanish [11] and African populations [12]. LEP G2548A single nucleotide polymorphism (rs7799039) is a guanine-adenine replacement at -2548 in the 5' promoter of the LEP gene [13]. According to Jiang et al. [14], this variant is not present in a conserved region of the genome between human, mouse, and rat species and indicated that its functional importance is unclear. However, the polymorphism is at the 5' promoter of the LEP gene [15], which is a location suggested to contain the inhibitory regulatory elements of adipocyte transcriptional activity [16]. Even though the G2548A mutation is located close to such regulatory features and a possible binding site of transcription factors, its direct impact on the expression of the leptin gene is not thoroughly proven.

OXIDATIVE STRESS IN PCOS

Oxidative stress (OS) has a primary role in the pathophysiology of ovulation disorders in PCOS by combining with hyperandrogenism, insulin resistance and obesity to create a vicious circle of pathogenesis. It has been shown that women with PCOS have high concentrations of reactive oxygen and nitrogen species and low antioxidant defences, which subsequently cause dysfunction of cells, mitochondrial damage, and a dysfunctional follicular microenvironment. This redox could stimulate overproduction of androgen by activating theca-interstitial cells and inhibiting sex hormone-binding globulin, and at the same time,

enhances insulin resistance by inflammatory signalling pathways and serine phosphorylation of insulin receptor substrates. Oxidative stress, hyperandrogenism and hyperinsulinemia all combined impact the normal development of follicles, arresting antral follicle development and compromising oocyte quality which leads to anovulation. In addition, obesity and overweight also increase oxidative stress by increasing the inflammation of adipose tissue and disregarding adipokine release, which exacerbates reproductive and metabolic dysfunction in PCOS. Taken together, these results indicate oxidative stress as one of the most

important mechanistic connections between metabolic anomalies and ovulatory failure in PCOS, which in turn justifies its importance as a possible therapeutic approach. The occurrence of oxidative stress is due to the lack of balance between the production of ROS and antioxidant defences. One important factor is oxidative stress in causing follicular apoptosis, insulin resistance, and inflammatory processes in PCOS. Increased malondialdehyde (MDA) and hydrogen peroxide (H₂O₂) are always reported, and the antioxidant enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GPx) are lower [17,18]

Table 1. Oxidative Stress Biomarkers in PCOS Populations

Biomarker	Type	Observation in PCOS
Malondialdehyde (MDA)	Lipid peroxidation marker	↑ Increased
Superoxide dismutase (SOD)	Antioxidant enzyme	↓ Decreased
Hydrogen peroxide (H ₂ O ₂)	ROS marker	↑ Elevated
Vitamin C & E	Non-enzymatic antioxidants	↓ Reduced

INTERPLAY BETWEEN LEPTIN POLYMORPHISMS AND OXIDATIVE STRESS

The interrelationship between the leptin polymorphism and oxidative stress is a significant point in the pathogenesis of metabolic and cardiovascular diseases. Leptin is a satiety hormone secreted by adipose tissue which may be used as a pro-inflammatory cytokine that stimulates the formation of reactive oxygen species (ROS), and particular genetic changes in the genes that encode leptin (LEP) and its receptor (LEPR) can mediate this risk.

Leptin dysregulation- which is in most cases the result of such genetic variations-enhances oxidative stress in a variety of ways:

- **Inflammatory Induction:** The changes in the *LEP* gene (such as rs7799039) are associated with the elevation of inflammatory indicators (such as TNF-alpha and IL-2) which are known to stimulate ROS generation.
- **Imbalance in Antioxidants:** Total Antioxidant Capacity (TAC) significantly drops in PCOS patients with the following genetic predispositions and reduced levels of antioxidant enzymes such as Superoxide Dismutase (SOD) and Catalase.
- **Marker Elevation:** Research indicates that there is a direct relationship between the genetic attributes of leptin and high levels of leptin the genetic markers of lipid peroxidation, like the Malondialdehyde (MDA) and Myeloperoxidase (MPx).

- Increased ROS (induced by hyperleptinemia) may cause tissue damage in the ovaries disrupting the FSH/LH signalling and the maturation of follicles. According to recent studies, there may be a reciprocal link between the leptin gene variations and oxidative disequilibrium. Leptin stimulates the production of NADPH oxidase and mitochondrial ROS, and oxidative stress suppresses leptin receptors phosphorylation and downstream JAK-STAT signalling.[19]. Some studies across the world have compared the *LEP* gene polymorphisms particularly the promoter variant-rs7799039 (G2548A) with PCOS susceptibility. Findings are not consistent for populations. There are reports of genotype or allele frequency differences between PCOS cases and controls, and others that do not form a direct association with the risk of PCOS. These variations are mostly due to ethnic differences, variations with respect to sample size and heterogeneity of clinical phenotypes. Even though the association of the association between rs7799039 and the susceptibility to PCOS is not always reliable, in certain populations, it has been associated with altered leptin levels, obesity, and metabolic disorders, demonstrating an indirect effect on PCOS pathophysiology. Besides *LEP*, *LEPR* polymorphisms, especially rs1137101 (Gln223Arg), are also quite popular. PCOS is not significantly related to individual research in Caucasian and Middle Eastern populations. Nevertheless, studies on East Asian communities have documented the links between *LEPR* variants and the risks of PCOS or associated metabolic characteristics.

According to meta-analyses, LEPR polymorphisms do not have a significant impact on the PCOS risk among the general population, though among the Asian subgroups, the genetic effects reveal significant associations. [20]

The literature of Indian research on LEP polymorphisms is limited; however, it becomes more and more topical in the conditions of the high rates of PCOS and metabolic syndrome among Indian women. A study conducted in South India has shown that the LEP rs7799039 G2548A polymorphism is linked to changes in metabolic parameters, oxidative stress biomarkers, and serum leptin levels of women with PCOS. These results imply that LEP variants might have a moderating effect on metabolic and oxidative stress pathways that are a key cause of PCOS progression instead of being

the cause. Nevertheless, limited research on LEPR polymorphisms in the Indian PCOS cohort has been conducted.

Altogether, international and domestic data indicate that LEP and LEPR polymorphisms play a population- and circumstances-dependent role in PCOS development largely due to interactions with obesity, insulin resistance, and oxidative stress. These incongruent results highlight the necessity of large-scale, well-designed research in different ethnic groups especially in India, which combines genetic information with hormonal, metabolic and environmental factors. These methods can contribute to understanding the role of leptin signalling in PCOS and assist in the evaluation and management of risks based on individuals and their aspects of risk assessment and management. [21]

Table 2: Global and Indian Studies on LEP Polymorphisms in PCOS

Study	Population	Polymorphism	Key Findings
Escobar-Morreale et al., 2003 [22]	Spain	-2548G/A	A-allele linked to higher leptin and BMI
Chou et al., 2008 [23]	Taiwan	-2548G/A	Association with insulin resistance
Zhao et al., 2023 [24]	China	LEP, LEPR	Leptin via JAK1/STAT3 promotes granulosa inflammation

PCOS is a multifactorial, intricate endocrine condition, which is a significant reproductive, metabolic and psychological health problem of women of reproductive age in the globe. The fact that it manifests itself heterogeneously, with menstrual irregularities and hyperandrogenism, down to infertility and metabolic dysfunction, indicates the complex interaction between genetic inclination, hormonal, environmental, and lifestyle factors. The prevalence rate of PCOS is quite high and fluctuates among the Indian and global populations and hence makes the need to conduct research and standardised methods of diagnostic techniques essential in ensuring an accurate identification and management of the acquired disease. The central role played by adipokines in mediating between metabolic aberrations and reproductive dysfunction in PCOS is also emerging. The leptin gene (LEP) is a well-regulated energy homeostasis, insulin-sensing, immune-controlling, and reproductive physiology gene. The changes in leptin signalling, either as a result of hyperleptinemia or leptin resistance, or as a result of genetic polymorphisms, also play a role in the pathogenesis of PCOS. The most popular of these is the LEP promoter region -2548G/A (rs7799039) which has been extensively examined as possibly having an effect on leptin expression, adiposity, insulin resistance and predisposition to PCOS, especially in various ethnic groups. Oxidative stress has been identified as a second important mechanistic factor

of PCOS as it is both a causal and a consequence of metabolic and hormone imbalances. The high level of reactive oxygen species and the inability to respond against them affect the ovarian follicular development, oocyte quality, and worsen the insulin resistance and chronic inflammation. The combination of oxidative stress with hyperandrogenism, obesity and insulin resistance is a vicious circle that contributes to the continuation of anovulation, and exacerbates the long-term reproductive and metabolic prognoses in PCOS women. Notably, an increase in evidence indicates that there is a reciprocal and synergistic connection between polymorphisms of the leptin gene and oxidative stress in PCOS. Genetic differences in the leptin signalling cascade can predispose individuals to hyperleptinemia and leptin resistance which facilitate the responses of inflammatory and oxidative damages by activating the pathways of the mitochondria and the NADPH oxidase systems. On the other hand, oxidative stress may suppress the metabolic and reproductive dysfunction by inhibiting leptin receptor communications and transmitting JAK-STAT activation. This relationship offers a convergent pattern of relationship between genetic susceptibility, adiposity, inflammation and redox imbalance in PCOS pathophysiology. The implications of clinical and therapeutic significance of the understanding of this complex network are critical. It emphasises the necessity of an interdisciplinary management strategy that is aimed at hormonal

regulation and ovulation induction, metabolic health, oxidative stress, and inflammation via lifestyle change, pharmacological therapy, and possibly antioxidant or gene-targeted therapy. Moreover, the early risk stratification and individual approach to the treatment can be supported by the identification of some population-specific genetic markers like LEP polymorphisms. Finally, PCOS cannot be considered a reproductive problem but a systemic one. The overlap of dysregulation of leptin genes and one of the most significant is oxidative stress pathogenic axes that affects both metabolic and reproductive symptoms of PCOS. Further studies into the interactions of genetic and environmental factors and redox biology will be necessary to gain more insights into PCOS and enhance the health outcomes of the affected women in the long term. Leptin gene mutations, specifically, the -2548G/A type, are major factors in the regulation of leptin concentration, oxidative stress, and metabolic impairment in PCOS. The two-way communication between genetic predisposition and oxidative disequilibrium is a factor in insulin resistance, chronic inflammation, and ovarian malfunction. The knowledge of such a genetic-oxidative axis could be used in the identification of new biomarkers and the design of targeted treatment procedures to address the personalised treatment of PCOS.

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