

Genetic Variations of the Insulin Receptor (INSR) Gene in Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, yet its underlying mechanisms remain incompletely defined. Beyond its reproductive features, PCOS is strongly associated with metabolic disturbances, particularly insulin resistance. Notably, impaired insulin action is observed even in non-obese patients, suggesting that intrinsic biological factors contribute to this dysfunction.

Given the central role of the insulin receptor in regulating glucose homeostasis and cellular insulin signalling, genetic variation within the insulin receptor (INSR) gene has been investigated as a potential contributor to PCOS susceptibility and metabolic heterogeneity. Over the past two decades, multiple association studies have examined specific INSR polymorphisms in diverse populations. While some variants have been linked to altered insulin sensitivity and metabolic indices, findings have not been consistently replicated, and effect sizes appear modest.

This review critically examines the available evidence regarding INSR gene polymorphisms in PCOS. We outline the biological rationale for focusing on INSR, summarize genetic association data across populations, and discuss methodological and phenotypic factors that may account for conflicting results. A clearer understanding of how INSR variability influences metabolic expression in PCOS may help refine future research strategies and improve interpretation of genetic findings in this complex disorder.

Keywords: Polycystic ovary syndrome; insulin resistance; insulin receptor; INSR gene; genetic polymorphism; metabolic heterogeneity; insulin signalling

I. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age and represents one of the leading

causes of anovulatory infertility worldwide [1,2]. Although its clinical presentation has traditionally centered on menstrual irregularity and hyperandrogenism, growing evidence indicates that PCOS extends beyond ovarian dysfunction and involves significant metabolic disturbance [3].

Over time, diagnostic frameworks have evolved, broadening the recognized phenotypic spectrum of the condition [4]. As a result, PCOS is now understood as a heterogeneous disorder encompassing reproductive, endocrine, and metabolic components. This heterogeneity complicates both mechanistic interpretation and therapeutic strategy.

Among the metabolic abnormalities associated with PCOS, insulin resistance is particularly prominent. A substantial proportion of affected women demonstrate impaired insulin sensitivity compared with body mass index-matched controls [5,6]. Importantly, insulin resistance has been documented in both obese and lean individuals, suggesting that intrinsic biological mechanisms contribute to altered insulin action [7].

Hyperinsulinemia secondary to insulin resistance has direct endocrine consequences. Elevated insulin levels potentiate ovarian androgen production and suppress hepatic synthesis of sex hormone-binding globulin, thereby increasing circulating free androgen concentrations [8]. These interactions provide a mechanistic link between metabolic imbalance and reproductive dysfunction.

Despite the central role of insulin resistance in PCOS, clinical expression varies considerably. Some women exhibit pronounced metabolic impairment, whereas others maintain relatively preserved insulin sensitivity while meeting diagnostic criteria [9]. This variability implies that genetic susceptibility may influence the degree to which insulin signaling pathways contribute to the PCOS phenotype.

Given its pivotal role in mediating insulin action, the insulin receptor represents a biologically plausible candidate for investigation. Variations within the gene encoding the insulin receptor

(INSR) may modify receptor function or signaling efficiency and thereby influence metabolic expression in PCOS. Understanding the extent to which INSR polymorphisms contribute to phenotypic heterogeneity is therefore of significant clinical and biological interest.

Insulin Resistance in PCOS: Pathophysiological Context

Insulin resistance is widely regarded as a defining metabolic feature of PCOS, although its severity and prevalence vary among individuals. Multiple studies have demonstrated reduced insulin sensitivity in women with PCOS compared to matched controls, independent of overall adiposity [10,11]. These findings indicate that metabolic dysfunction in PCOS cannot be explained solely by excess body weight.

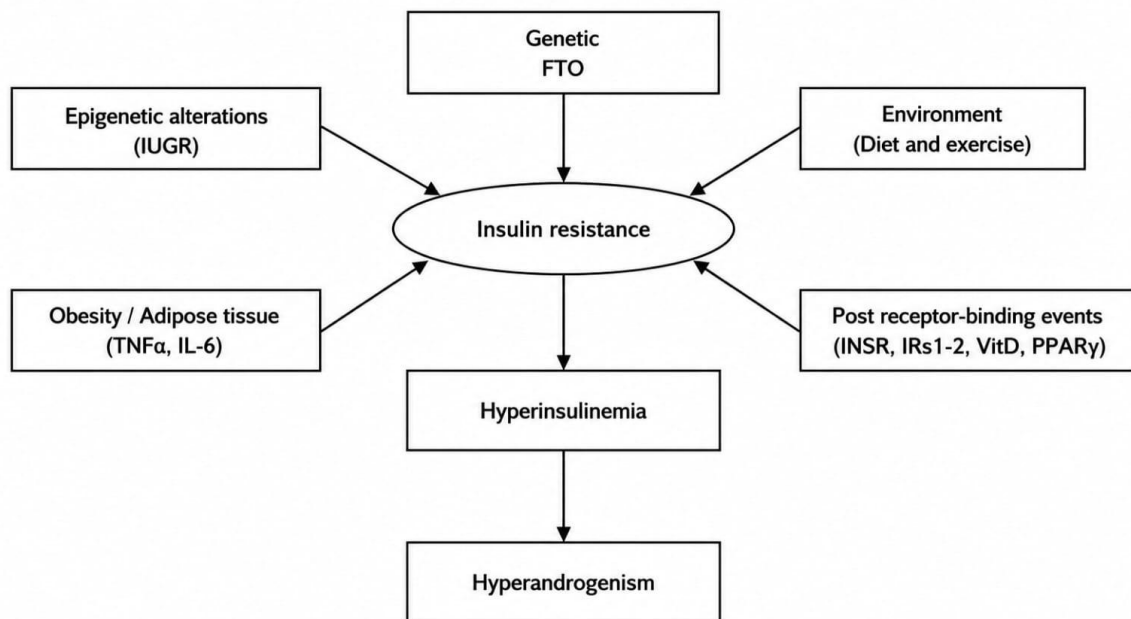


Fig 1. Pathways contributing to insulin resistance and development of hyperinsulinemia and hyperandrogenism in PCOS.

At the systemic level, impaired insulin responsiveness in skeletal muscle, adipose tissue, and liver results in compensatory hyperinsulinemia. Elevated insulin concentrations promote increased hepatic glucose production and altered lipid metabolism, contributing to long-term cardiometabolic risk [12]. These metabolic disturbances often precede overt glucose intolerance.

Importantly, insulin exerts direct effects on ovarian physiology. In theca cells, insulin enhances androgen synthesis and amplifies luteinizing hormone-stimulated steroidogenesis [13]. Concurrently, hyperinsulinemia suppresses hepatic production of sex hormone-binding globulin, leading to increased bioavailability of circulating androgens [14]. These mechanisms help explain the tight interrelationship between metabolic imbalance and reproductive dysfunction in PCOS.

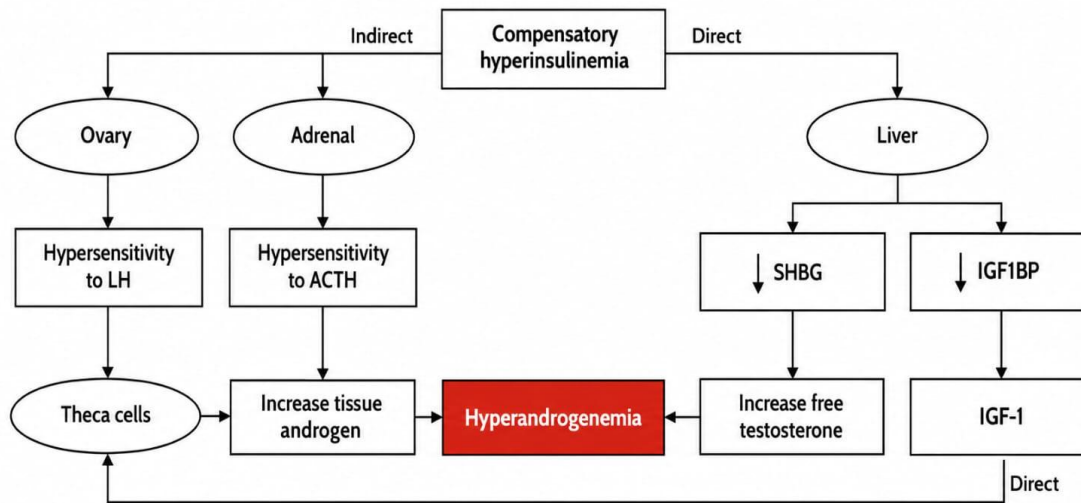


Fig 2. Direct and indirect mechanisms through which hyperinsulinemia contributes to hyperandrogenism in PCOS.

Notably, insulin resistance in PCOS does not appear to be uniform at the tissue level. Some studies suggest that while peripheral tissues such as muscle demonstrate impaired insulin signaling, ovarian tissue may retain relative sensitivity to insulin [15]. This selective responsiveness allows hyperinsulinemia to stimulate androgen production even in the presence of systemic metabolic resistance.

At the cellular level, abnormalities have been described in both receptor activation and post-receptor signaling pathways, including altered phosphorylation patterns and impaired downstream signaling efficiency [16]. Such findings support the concept that intrinsic alterations in insulin signaling contribute to PCOS pathophysiology.

However, significant heterogeneity exists. Some women with PCOS exhibit marked insulin resistance and metabolic impairment, whereas others maintain near-normal insulin sensitivity. This variability strongly suggests that genetic background, in interaction with environmental influences, modulates metabolic expression within the syndrome.

Given this context, investigation of genes directly involved in insulin signaling, particularly the insulin receptor gene, is a logical next step in understanding phenotypic diversity in PCOS.

Molecular Structure and Signalling of the Insulin Receptor

The insulin receptor is a transmembrane glycoprotein belonging to the receptor tyrosine kinase family. It is synthesized as a single precursor polypeptide that undergoes proteolytic cleavage to form two extracellular α -subunits and two transmembrane β -subunits, which assemble into a heterotetrameric $\alpha_2\beta_2$ complex [17]. The α -subunits are responsible for insulin binding, while the β -subunits contain the intracellular tyrosine kinase domain essential for signal propagation.

Binding of insulin to the extracellular domain induces conformational changes that trigger autophosphorylation of specific tyrosine residues within the β -subunit [18]. This phosphorylation enhances kinase activity and creates docking sites for adaptor proteins, particularly insulin receptor substrates (IRS proteins), which initiate downstream intracellular signaling cascades.

Two principal pathways mediate the biological effects of insulin. The phosphoinositide 3-kinase (PI3K)/Akt pathway primarily regulates metabolic actions, including glucose uptake, glycogen synthesis, and lipid metabolism [19]. In skeletal muscle and adipose tissue, activation of this pathway promotes translocation of glucose transporter type 4 (GLUT4) to the cell membrane, facilitating glucose entry into cells [20]. In contrast, the mitogen-activated protein kinase (MAPK) pathway is more closely associated with cellular growth and proliferative responses [21].

Dysregulation at any stage of this signaling cascade can impair insulin responsiveness.

Abnormal receptor phosphorylation and defects in downstream signaling components have been described in subsets of women with PCOS, suggesting intrinsic disturbances in insulin action [22]. These alterations may contribute to reduced peripheral glucose utilization while preserving or even enhancing insulin responsiveness in ovarian tissue.

Importantly, rare pathogenic mutations in the INSR gene are known to cause severe insulin resistance syndromes characterized by profound metabolic abnormalities [23]. Although PCOS does not typically involve such dramatic receptor dysfunction, these monogenic conditions underscore the critical role of the insulin receptor in maintaining metabolic homeostasis.

Given the central position of the insulin receptor at the apex of insulin signaling, even subtle genetic variation within INSR could potentially influence signaling efficiency and metabolic phenotype. This provides a strong biological rationale for examining INSR polymorphisms in the context of PCOS.

Genetic Architecture of the INSR Gene

The insulin receptor is encoded by the INSR gene located on chromosome 19p13.2. The gene spans more than 120 kilobases and comprises multiple exons encoding distinct structural domains of the receptor, including the extracellular ligand-binding region, the transmembrane segment, and the intracellular tyrosine kinase domain [24]. This genomic organization reflects the functional complexity of the receptor and allows for precise regulation of insulin signaling.

A notable feature of the INSR gene is alternative splicing of exon 11, which generates two principal isoforms commonly referred to as IR-A and IR-B [25]. These isoforms differ by a short peptide sequence within the α -subunit and exhibit distinct biological properties. IR-A demonstrates relatively higher affinity for insulin-like growth factors and is more frequently expressed in fetal and proliferative tissues, whereas IR-B predominates in classical metabolic tissues such as liver, skeletal muscle, and adipose tissue. Although the clinical implications of isoform distribution in PCOS are not fully established, differential expression patterns may influence tissue-specific insulin responsiveness.

In addition to rare pathogenic mutations associated with severe insulin resistance syndromes, numerous common single nucleotide polymorphisms (SNPs) have been identified throughout the INSR gene [26]. These variants are

distributed across coding regions, introns, and regulatory sequences. Polymorphisms located within exonic regions may theoretically alter amino acid composition or kinase activity, while intronic and promoter variants may influence transcriptional regulation, mRNA stability, or splicing efficiency [27].

It is essential to distinguish between rare high-penetrance mutations and common variants with modest functional impact. Monogenic disorders caused by deleterious INSR mutations present with profound insulin resistance and early-onset metabolic abnormalities [28]. In contrast, PCOS is widely considered a multifactorial and polygenic condition in which individual genetic variants are expected to exert relatively small effect sizes [29].

Therefore, common INSR polymorphisms investigated in PCOS are unlikely to produce overt receptor dysfunction. Rather, they may subtly modulate receptor expression or signaling efficiency and, in combination with other genetic and environmental factors, contribute to variability in metabolic phenotype.

This genetic framework provides the necessary background for evaluating association studies examining the relationship between specific INSR variants and PCOS susceptibility.

Association Studies of INSR Polymorphisms in PCOS

Frequently Investigated Variants

Several single nucleotide polymorphisms within the INSR gene have been examined in women with PCOS across diverse populations. Among these, the rs1799817 polymorphism located in exon 17 has received the greatest attention [30]. Because exon 17 contributes to the intracellular tyrosine kinase domain of the receptor, variation in this region is biologically plausible in the context of altered signaling efficiency.

Early case-control studies in Asian populations reported an association between rs1799817 and PCOS susceptibility, as well as with indices of insulin resistance such as fasting insulin levels and HOMA-IR [31,32]. In some cohorts, specific genotypes were associated with higher circulating insulin concentrations, suggesting a potential modulatory effect on metabolic phenotype rather than direct disease causation.

However, findings have not been consistent across populations. Investigations conducted in European cohorts failed to replicate significant associations between rs1799817 and PCOS risk after adjustment

for body mass index and other confounders [33,34]. These discrepancies highlight the modest effect size of this variant and suggest possible population-specific influences.

Beyond rs1799817, additional INSR polymorphisms have been explored. Variants located in intronic regions and regulatory sequences have been evaluated for associations with PCOS susceptibility and metabolic parameters [35,36]. While some studies reported statistically significant genotype–phenotype correlations, replication has been limited and results have varied between ethnic groups.

Ethnic Variability and Population Differences

Allele frequencies for INSR polymorphisms differ substantially among populations, and patterns of linkage disequilibrium vary accordingly [37]. This genetic background can influence whether a specific SNP serves as an effective marker for a functional variant within a given population.

Positive associations between certain INSR variants and PCOS have been reported in South Asian and Middle Eastern populations [38,39]. In contrast, studies in East Asian and European populations have yielded mixed or negative findings [34,40]. These differences emphasize the importance of considering ethnic background when interpreting genetic association data.

Meta-Analytic Evidence

To address inconsistencies across individual studies, several meta-analyses have evaluated pooled data on INSR polymorphisms and PCOS risk. These analyses suggest that rs1799817 and related variants may be associated with increased susceptibility in specific subgroups, particularly within Asian populations [41]. However, overall effect sizes are small, and significant heterogeneity between studies has been reported.

Sensitivity analyses frequently demonstrate that associations weaken when smaller studies are excluded or when analyses are restricted to high-quality cohorts [42]. This pattern indicates that publication bias or limited statistical power may contribute to reported positive findings.

Genotype–Phenotype Associations

Importantly, some investigations suggest that INSR polymorphisms may be more strongly associated with metabolic features within PCOS rather than with diagnostic status alone [43]. For example, certain variants have been linked to fasting insulin levels, insulin resistance indices, or lipid profile alterations in women with PCOS.

This distinction is critical. PCOS represents a heterogeneous syndrome encompassing multiple phenotypes. Failure to stratify patients according to metabolic severity may obscure meaningful associations between genotype and metabolic expression [44].

Taken together, current evidence suggests that INSR polymorphisms are unlikely to serve as primary causal determinants of PCOS. Instead, they may function as susceptibility modifiers that influence metabolic variability within a broader polygenic framework.

Methodological Considerations and Limitations of Current Evidence

Interpretation of genetic association studies examining INSR polymorphisms in PCOS requires careful consideration of methodological constraints. Several recurring limitations likely contribute to the variability and inconsistency observed across published findings.

One of the most common limitations is modest sample size. Many case–control studies investigating INSR variants have included relatively small cohorts, which reduces statistical power and increases susceptibility to both false-positive and false-negative associations [31,33]. In complex polygenic disorders such as PCOS, where individual variants are expected to exert small effect sizes, inadequate power can substantially distort observed relationships.

Diagnostic heterogeneity represents another important challenge. PCOS can be defined using different criteria, and not all studies clearly specify or uniformly apply these definitions. Variability in diagnostic framework may lead to inclusion of phenotypically diverse patient groups, thereby weakening the ability to detect true genotype–phenotype associations [34].

Population stratification further complicates interpretation. Allele frequencies and linkage disequilibrium patterns differ across ethnic groups, and associations identified in one population may not replicate in another [37]. The mixed findings reported across Asian, European, and Middle Eastern cohorts underscore the importance of replication in ethnically diverse and adequately powered samples.

In addition, several studies have focused primarily on diagnostic status rather than detailed metabolic phenotyping. As discussed earlier, INSR polymorphisms may influence metabolic severity more strongly than overall PCOS susceptibility [44]. Failure to stratify patients by insulin resistance

indices or metabolic parameters may obscure meaningful associations.

Meta-analyses have attempted to address inconsistencies by pooling data; however, significant heterogeneity between studies persists, and effect sizes remain modest [41,42]. Sensitivity analyses often demonstrate attenuation of associations after exclusion of smaller or lower-quality studies, suggesting potential publication bias or methodological variability.

Finally, functional validation of reported associations remains limited. Although statistical correlations between specific INSR variants and metabolic markers have been described, direct experimental evidence demonstrating altered receptor expression or signaling efficiency is scarce. Without mechanistic confirmation, causal inference remains tentative.

Taken together, these methodological considerations indicate that current evidence supports a contributory rather than deterministic role for INSR polymorphisms in PCOS. Future investigations would benefit from larger multi-center cohorts, consistent diagnostic criteria, detailed metabolic characterization, and functional validation of candidate variants.

Integrating Molecular and Clinical Evidence

The biological plausibility linking INSR polymorphisms to PCOS is clear. The insulin receptor occupies a central position in metabolic signaling, and even modest alterations in receptor function could theoretically influence insulin sensitivity and downstream endocrine effects. Given the well-established role of insulin resistance in the pathophysiology of PCOS [6], investigation of genetic variability within INSR is conceptually justified.

However, clinical evidence suggests that PCOS is not characterized by overt insulin receptor dysfunction comparable to rare monogenic insulin resistance syndromes. Instead, metabolic abnormalities in PCOS are typically moderate and variable. Genome-wide and candidate gene studies increasingly support the view that PCOS is a complex polygenic disorder involving multiple interacting pathways rather than a condition driven by a single major gene effect [12].

Within this broader framework, INSR polymorphisms appear to exert modest and, in many cases, population-specific effects [41]. Associations are often stronger when metabolic parameters are considered as continuous traits rather than when disease status alone is examined [44]. This pattern is

consistent with a model in which INSR variants function as susceptibility modifiers that influence metabolic expression rather than as primary determinants of disease.

Thus, current evidence supports a nuanced interpretation. INSR genetic variability likely contributes to inter-individual differences in insulin responsiveness within PCOS, but it does not independently account for the heterogeneity of the syndrome. Appreciating this distinction is essential for avoiding overstatement of genetic findings while recognizing their potential relevance within the broader biological context.

II. Conclusion

Polycystic ovary syndrome is a heterogeneous disorder in which metabolic and reproductive abnormalities are closely intertwined. Insulin resistance remains a central component of its pathophysiology and contributes significantly to both endocrine imbalance and long-term metabolic risk [6]. However, the severity of insulin resistance varies substantially among affected individuals, underscoring the complexity of the syndrome.

Genetic investigation of the insulin receptor gene is biologically justified given its pivotal role in insulin signaling. Available evidence indicates that common INSR polymorphisms may influence metabolic parameters in certain populations. Nevertheless, reported associations are generally modest, often population-specific, and not consistently replicated [41].

Current understanding of PCOS increasingly supports a polygenic model involving multiple interacting pathways rather than a single dominant genetic determinant [12]. Within this framework, INSR variants likely function as susceptibility modifiers that contribute to metabolic heterogeneity rather than as primary causal factors.

Overall, the existing literature supports a contributory but limited role for INSR genetic variability in PCOS. Careful interpretation of association data, combined with improved study design and functional validation, will be essential for clarifying the precise contribution of insulin signaling genes to this complex disorder.

Statements and Declaration

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Conflict of Interests

The authors declare that they have no competing interests.

Author Contribution

Saral Jasmin Santhoshini A developed the conceptual framework of the review, conducted the literature search, analyzed and organized the collected data, and prepared the initial manuscript draft. Thomas Santhoshni J contributed to literature collection, manuscript refinement, formatting, and critical review of the content. Dr. M. Chamundeeswari provided academic guidance, supervision, critical insights, and final revisions to improve the scientific quality of the manuscript. All authors reviewed and approved the final version of the manuscript.

Data Availability

Not Applicable

Reference

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