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Hereditary Genetic Mutations in Polycystic Ovary Syndrome (PCOS): Current State of the Problem

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, with a prevalence of 5-15% depending on the diagnostic criteria used. Clinically, the syndrome is characterized by hyperandrogenism and ovulatory dysfunction and is frequently accompanied by insulin resistance, obesity, and an increased risk of type 2 diabetes mellitus. Genealogical and twin studies indicate high heritability of PCOS (70-80%), which has stimulated active investigation of genetic factors. In recent years, genome-wide association studies (GWAS) have identified dozens of loci associated with PCOS risk, including *DENND1A*, *LHCGR*, *FSHR*, *THADA*, *INSR*, *YAP1*, *GATA4,* and *AMH/AMHR2*. The present review summarizes current data (2018-2025) on hereditary genetic variants in PCOS, analyzing their functional roles in the regulation of the gonadotropic axis, metabolic pathways, and steroidogenesis. We discuss how genetic variability contributes to the phenotypic heterogeneity of the syndrome – ranging from predominantly reproductive to pronounced metabolic forms. Along with common polymorphisms, rare variants associated with familial and atypical cases of PCOS are also reviewed. Finally, we evaluate the prospects for clinical application of the knowledge gained, including the development of polygenic risk scores and personalized treatment strategies, as well as discussing the limitations of current GWAS and controversies in the interpretation of their findings.

Keywords: Polycystic ovary syndrome, GWAS, Hyperandrogenism, *DENND1A*, Insulin resistance, Polygenic disease

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder affecting 5-15% of women of reproductive age, making it one of the most common gynecological conditions (Pereira-Eshraghi & Vuguin, 2024; Dokras, 2025; Helvaci & Yildiz, 2025). The clinical presentation of PCOS involves three core components: chronic anovulation, signs of hyperandrogenism (hirsutism, acne, alopecia), and characteristic ultrasound findings – enlarged ovaries with multiple small antral follicles (Peña & Witchel, 2025; Su *et al*., 2025). Beyond these features, a wide range of metabolic abnormalities are frequently present, including insulin resistance, compensatory hyperinsulinemia, dyslipidemia, and a markedly increased risk of type 2 diabetes mellitus (Agrawal *et al*., 2023; Zhao *et al*., 2023; Zhang *et al*., 2025).

The etiology of PCOS has remained incompletely understood for several decades. On one hand, well-recognized environmental triggers include excess body weight, physical inactivity, and dietary patterns. On the other hand, substantial evidence points to a significant role of heredity. As early as the end of the last century, data were published showing that 30-40% of mothers and sisters of PCOS patients exhibit endocrine abnormalities similar to those seen in the syndrome (Huddleston & Dokras, 2022; Zhao *et al*.,

2026). Twin studies, particularly from the Dutch twin registry, have estimated the heritability of PCOS at approximately 70%, which is considerably higher than that of many other multifactorial disorders (Welt, 2021; Louwers *et al*., 2025).

For a long time, the search for specific genetic markers of PCOS relied on the "candidate gene" approach. Investigators examined polymorphisms in genes involved in steroidogenesis (*CYP11A*, *CYP17*, *CYP19*), insulin metabolism (*INSR*, *IRS1*, *IRS2*), androgen action (*AR*, *SRD5A2*), and gonadotropin signaling (*FSHR*, *LHCGR*) (Azevedo *et al*., 2020; Alyousif *et al*., 2024; Chang *et al*., 2024). Unfortunately, the results of these studies were often contradictory and, with few exceptions, could not be replicated in independent cohorts (Jamshidi *et al*., 2021; Zhou *et al*., 2021).

A breakthrough came with the introduction of genome-wide association studies (GWAS). In parallel, increasing research interest has also been directed toward plant-derived bioactive compounds and their potential modulatory effects on metabolic and endocrine pathways, although their role in complex disorders such as PCOS remains unclear (Hamad *et al*., 2018; Ahmed *et al*., 2020). This method allows unbiased scanning of the entire genome for common variants that are statistically associated with a disease, without requiring prior hypotheses. The first GWAS of PCOS was performed in 2011 in a Chinese population (Islam *et al*., 2022). Even that initial study yielded unexpected results, pointing to loci that had not previously been considered in the context of PCOS (e.g., *DENND1A*). Subsequent GWAS, including those in European populations and large-scale meta-analyses, expanded the list of associated loci to several dozen, and in 2025 to 94 (Zhu & Goodarzi, 2022; Zhao *et al*., 2026).

This review aims to summarize current knowledge on the genetic architecture of PCOS, describing the main genes and variants associated with the syndrome, their functional roles, and their implications for understanding pathogenesis. Special attention is given to comparing GWAS findings with the clinical heterogeneity of the syndrome and to analyzing discrepancies between results obtained in different population studies.

General Characteristics of Genetic Loci Associated with PCOS

To date, international consortia have reached a consensus on approximately 19-30 loci that are reliably associated with the risk of developing PCOS across different populations (Joo *et al*., 2020; Siddiqui *et al*., 2022; Dong & Rees, 2023). The largest study to date, published in 2025, increased this number to 94, of which 73 were described for the first time (Zhao *et al*., 2025). The vast majority of identified variants have small effect sizes, with odds ratios typically ranging from 1.1 to 1.3 (Larsen *et al*., 2023; Samma *et al*., 2024). This pattern is typical of polygenic disorders, in which the phenotype arises from the cumulative action of many genetic "building blocks", each contributing only modestly.

An exception is rare variants (minor allele frequency <1%), which are poorly captured by GWAS by design. Such variants, identified in the *DENND1A*, *AMH* and *AMHR2* genes through whole-genome sequencing, may have larger effects and can even underlie familial forms of PCOS (di Clemente *et al*., 2022; van der Ham *et al*., 2024).

All identified loci can be grouped into functional categories, helping to clarify which biological processes are most vulnerable in this syndrome. A summary diagram of the functional clustering of key genes is presented in **Figure 1**.

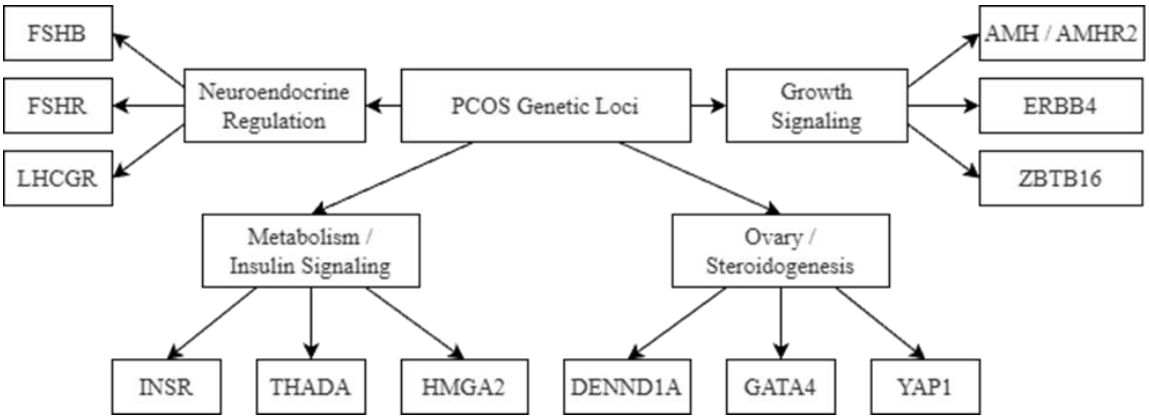

Figure 1. Functional clustering of genes associated with PCOS

Key Genes and Their Functional Groups

Genes controlling the gonadotropic axis. Locus 2p16.3, which harbors the genes for the luteinizing hormone receptor (*LHCGR*) and the follicle-stimulating hormone receptor (*FSHR*), is among the most consistently replicated findings across different GWAS (Gao *et al*., 2025; Singh *et al*., 2025). The rs13405728 polymorphism in *LHCGR* is associated with higher testosterone levels and ovulatory disturbances. Another important locus lies in the promoter region of the *FSHB* gene (11p14.1). The rs11031006 variant is linked to reduced FSH levels and a relative increase in LH, thereby creating the characteristic LH/FSH ratio seen in PCOS (Kiewa *et al*., 2023; Kordes & Busch, 2026). Thus, genetic evidence now supports a long-recognized clinical phenomenon – the gonadotropin imbalance in PCOS.

Genes Involved In Metabolism and Insulin Sensitivity

Locus 19p13.3, which contains the insulin receptor gene (*INSR*), has been consistently associated with PCOS across studies of different ethnic groups (Tenorio *et al*., 2020; Taskin & Eroğlu, 2025). This finding is notable from a historical perspective: as early as the 1980s, severe forms of hyperandrogenism were linked to *INSR* mutations, and hyperinsulinemia was postulated to play a role in typical PCOS (Zhong *et al*., 2021; Saedi *et al*., 2025). GWAS have confirmed that even common polymorphisms of this gene contribute to the predisposition to insulin resistance. (Thazha *et al*., 2023; Al-Twaijri *et al*., 2024; Ansari *et al*., 2024; Feng *et al*., 2024; Jeung, 2024; Landry *et al*., 2024; Suchy & Jurkowski, 2024).

Another important locus is 2p21, where the *THADA* gene is located. Initially known for its role in thyroid adenomas, *THADA* was later found to participate in the regulation of energy metabolism and apoptosis (Tyrmi *et al*., 2022; Velmurugan *et al*., 2024). Variants in *THADA* are also associated with the risk of type 2 diabetes, indicating a shared genetic basis for the two conditions (Tian *et al*., 2020; Azumah *et al*., 2023). Similarly, polymorphisms in the *HMGA2* gene (12q14.3), which influence adipogenesis, link PCOS to obesity (Jiao *et al*., 2018; Li *et al*., 2019).

Genes Modulating Steroidogenesis and Ovarian Function

The most striking and possibly most PCOS-specific gene is *DENND1A* (9q33.3). It encodes a protein involved in endosomal trafficking, yet it unexpectedly emerged as a key regulator of androgen production in theca cells (Gao *et al*., 2016; Wan *et al*., 2021). In *in vitro* experiments, increased expression of *DENND1A* led to a marked enhancement of testosterone synthesis (Sudhakaran *et al*., 2023; Sankaranarayanan *et al*., 2025).

More recently, the genes *AMH* and its receptor *AMHR2* have attracted attention. Contrary to the classical view that anti-Müllerian hormone (AMH) levels are elevated in PCOS, rare mutations that reduce AMH signaling pathway activity have been detected in 6-7% of patients (di Clemente *et al*., 2022; Moolhuijsen *et al*., 2022; van der Ham *et al*., 2024). Carriers of such variants typically have normal or even low AMH levels, which defines a distinct, non-classical variant of the syndrome (Piltonen *et al*., 2023; Laven, 2025). Key genes associated with PCOS according to GWAS, along with their proposed biological functions and links to the phenotype, are summarized in **Table 1**.

Table 1. Major genes/loci associated with PCOS (GWAS) and their proposed roles

Gene/locus	Biological pathway	Pathogenetic effect in PCOS	Phenotypic association
***LHCGR* (2p16.3)**	LH/hCG receptor	↑ Theca cell sensitivity to LH → ↑ androgens	Hyperandrogenism, anovulation
***FSHR* (2p16.3)**	FSH receptor	↓ granulosa cell response to FSH	Oligomenorrhea, poor follicular growth
***FSHB* (11p14.1)**	FSH secretion (pituitary)	Genetically driven ↓ FSH and relative ↑ LH	↑ LH/FSH ratio, anovulation
***DENND1A* (9q33.3)**	Endosomal trafficking, theca cells	↑ androgen production (key driver)	Early/severe hyperandrogenism, family history
***THADA* (2p21)**	Energy metabolism, thermogenesis	Impaired metabolic adaptation	Obesity, insulin resistance, dyslipidemia
***INSR* (19p13.3)**	Insulin receptor	Hereditary predisposition to insulin resistance	Metabolic phenotype: IR, prediabetes
***HMGA2* (12q14.3)**	Adipogenesis, cell growth	↑ propensity for adipose tissue accumulation	Obesity / high BMI, exacerbated IR
***YAP1* (11q22.1)**	Hippo pathway (proliferation)	Disrupted follicular growth control	Polycystic ovarian morphology, chronic anovulation
***GATA4* (8q23.1)**	Transcription, gonadal development	Subtle shifts in steroidogenesis	Anovulation, variable hyperandrogenism
***AMH / AMHR2* (19p13 / 12q13)**	Folliculogenesis, AMH signaling	Imbalance of CYP17 inhibition (common and rare variants)	Altered follicular dynamics, anovulation
***ZBTB16* (11q23.2)**	Transcription, differentiation	Protective effect (OR ~0.8)	Trend toward reduced PCOS risk

Other Significant Loci

In European populations, the association of PCOS with locus 8q23.1 has been confirmed; this region contains the transcription factor *GATA4*, an important regulator of gonadal development and steroidogenesis (Wang *et al*., 2019; Dharani *et al*., 2025). Locus 11q22.1 harbors the *YAP1* gene, which participates in the Hippo signaling pathway that controls cell proliferation and organ size; its hyperactivation may promote the formation of multiple cystic follicles (Zhang *et al*., 2023; Xu *et al*., 2026). Also of interest is locus 11q23.2 with the *ZBTB16* gene, which in some analyses has been associated with a reduced risk of PCOS (OR ~0.8), suggesting the existence of protective alleles (Yang *et al*., 2020; Tidwell *et al*., 2024).

Rare Variants and Familial Forms of PCOS

As noted earlier, GWAS are designed to detect common variants with small effect sizes. Identifying rare variants (MAF < 1%) requires different approaches, particularly exome or genome sequencing in families with multiple PCOS cases. Using such methods, it has been shown that rare mutations in *DENND1A* are found in approximately half of families where several women are affected by PCOS and may account for monogenic/oligogenic forms of the disease (Branavan *et al*., 2019; Crespo *et al*., 2022). Similarly, 6-7% of PCOS patients (not necessarily familial) carry rare variants in *AMH* and *AMHR2* that disrupt the signaling pathway (di Clemente *et al*., 2022; Ke *et al*., 2025).

These findings carry important conceptual implications: they demonstrate that a clinically similar PCOS phenotype can arise from different genetic mechanisms – ranging from the polygenic accumulation of many weak-effect variants to rare mutations with relatively large effects. The most extensively studied rare variants associated with familial and atypical forms of PCOS are summarized in **Table 2**. The interplay between different groups of genetic factors and their contribution to key pathogenetic pathways and phenotypic manifestations of PCOS is schematically illustrated in **Figure 2**.

Table 2. Rare genetic variants with suspected monogenic/oligogenic effects in PCOS

Gene	Variant type	Frequency in PCOS patients	Functional effect	Phenotypic association
DENND1A	Missense variants, splicing defects	~1-2% (up to 50% in familial cases)	↑ androgen synthesis in theca cells	Severe hyperandrogenism, family history
AMH	Heterozygous rare variants	~3-4%	↓ AMH signaling, derepression of CYP17	Anovulation without elevated AMH
AMHR2	Heterozygous rare variants	~3-4%	↓ sensitivity to AMH	Anovulation, variable AMH levels
FSHR	Rare variants (e.g., p.Ala189Val)	<1%	↑ or ↓ sensitivity to FSH	Impaired folliculogenesis
LHCGR	Rare activating variants	<1%	↑ basal receptor activity	Precocious puberty, hyperandrogenism

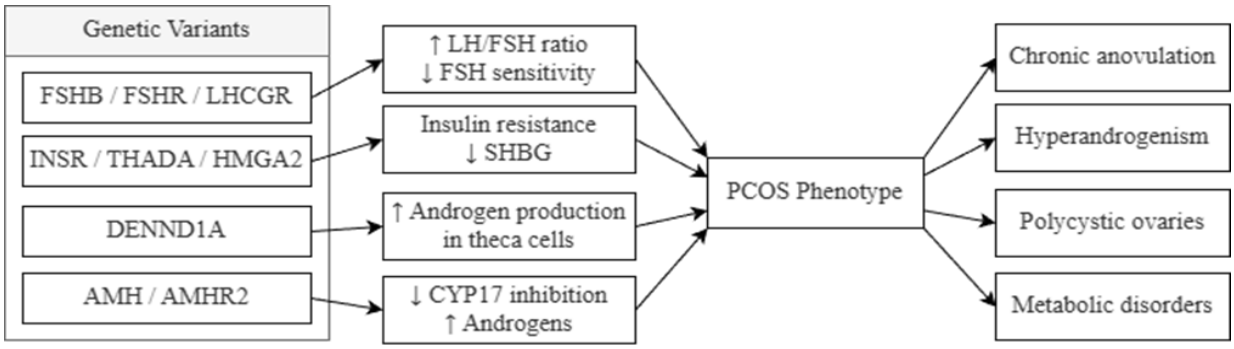

Figure 2. Interaction of genetic factors and pathogenetic pathways in PCOS

Results and Discussion

The data presented in this review clearly indicate that PCOS is a polygenic disorder with a complex, multi-layered genetic architecture. There is broad consensus in the literature that no single gene or variant determines the development of the syndrome in the majority of patients. However, behind this consensus lie several unresolved issues and methodological limitations that deserve separate consideration. Instead, risk is shaped by the cumulative effect of many dozens, and likely hundreds, of alleles, each contributing a modest effect (Dapas *et al*., 2020; Asadi *et al*., 2023; Zhang & Yu, 2024; Almotairi *et al*., 2025; Venkatesh *et al*., 2025). This explains both the high heritability (approximately 70%) and the inability to identify a single causal factor.

Pathogenetic Interpretation of Genetic Findings

Clustering of the identified loci allows delineation of three main biological nodes whose disruption underlies PCOS.

First node – neuroendocrine dysregulation. Genetic variants in FSHB, FSHR, and LHCGR create a predisposition to increased gonadotropin-releasing hormone (GnRH) pulse frequency in the hypothalamus, leading to excessive LH secretion and relative FSH deficiency (McCartney *et al*., 2022; Wang *et al*., 2023; Yang & Chen, 2024; Moore, 2025). The clinical consequence is stimulation of androgen production in theca cells and impaired maturation of the dominant follicle. Some authors suggest that genotyping of these loci may eventually help predict response to ovulation induction, although this hypothesis requires validation (Siddamalla *et al*., 2020; Zhu *et al*., 2025).

Second node – metabolic disturbances. The genetic association of PCOS with INSR, THADA, and HMGA2 confirms the long-standing clinical observation that the syndrome frequently coexists with obesity and insulin resistance (Rosenfield & Dumesic, 2016; Ali *et al*., 2022; Sánchez-Garrido *et al*., 2024). Depending on whether metabolic or neuroendocrine genetic variants predominate in an individual's risk profile, either reproductive or metabolic features may dominate. Thus, two extreme phenotypes have been described: "reproductive" (marked hyperandrogenism and anovulation in normal-weight women) and "metabolic" (moderate hyperandrogenism伴随 pronounced obesity, dyslipidemia, and prediabetes) (Witchel *et al*., 2019; Zeng *et al*., 2020; Sánchez-Garrido & Tena-Sempere, 2020; Rashid *et al*., 2022). Between these poles lies a continuum of transitional forms.

Third node – intraovarian mechanisms of hyperandrogenism. The discovery of DENND1A was a turning point in understanding that increased androgen production can be not only secondary (a consequence of elevated LH or hyperinsulinemia) but also primary and genetically determined. Functional studies have convincingly demonstrated that regulatory variants in *DENND1A* can directly enhance steroidogenesis in theca cells (Indran *et al*., 2016; Dapas *et al*., 2019; Rosenfield & Dumesic, 2025). Rare mutations in this gene, identified in familial cases, have considerably larger effects than common GWAS variants and may underlie oligogenic forms of PCOS (Topaloğlu, 2017; Afzal *et al*., 2021; Branavan *et al*., 2021). Similarly, the detection of rare variants in *AMH/AMHR2* that reduce signaling pathway activity in 6-7% of patients unexpectedly showed that even such a classic marker as AMH is not universal across all PCOS cases (Castillo-Higuera *et al*., 2021; Komorowski *et al*., 2024; Choi *et al*., 2026).

Limitations of Current Genetic Studies

Despite undeniable progress, many questions remain open. The aggregate heritability of PCOS explained by identified common variants does not exceed 10% (Xue *et al*., 2015). This phenomenon, known as "missing heritability," is characteristic of most polygenic disorders. The most likely explanations include: (1) contributions from rare variants not captured by standard GWAS; (2) epigenetic mechanisms (methylation, histone modifications, non-coding RNAs); (3) gene-gene and gene-environment interactions that cannot yet be adequately modeled (Rosenfield & Dumesic, 2016; Rosenfield & Ehrmann, 2016; Stener-Victorin & Deng, 2021).

The epigenetic aspect deserves particular attention. Experimental models have shown that in utero androgen exposure induces lasting epigenetic changes in female offspring, predisposing them to a PCOS-like phenotype (Sagvekar *et al*., 2018; Bruni *et al*., 2022). Indirect human evidence also exists: daughters of women with PCOS have higher AMH levels and accelerated adrenarche (Burt Solorzano & McCartney, 2021). This opens perspectives for studying epigenetic markers as early predictors of the disease (Thazha *et al*., 2023; Bandi *et al*., 2024; Essah *et al*., 2024; Frost *et al*., 2024; Jeung, 2024; Landry *et al*., 2024; Uneno *et al*., 2024).

One of the most intriguing contradictions remains the discrepancy between the high heritability of PCOS (70-80%) and the low fraction explained by GWAS (<10%). This gap, characteristic of other polygenic diseases as well, may, in the case of PCOS, point to a substantial role of rare variants, structural rearrangements, or non-linear gene-gene interactions that are not captured by standard methods. Some authors also suggest that the phenotypic criteria used (Rotterdam, NIH) may "dilute" genetic associations by combining etiologically distinct subgroups of patients (Simonyan *et al*., 2023; Tsiganock *et al*., 2023; Ku *et al*., 2023; Genc *et al*., 2023; Delcea *et al*., 2024; Essah *et al*., 2024; Sanlier & Yasan, 2024; Ribeiro *et al*., 2024; Uneno *et al*., 2024).

Prospects for Clinical Application

Currently, routine genetic testing is not recommended for the diagnosis or treatment of PCOS (Vishnubotla *et al*., 2020; Doulgeraki *et al*., 2023; Lai *et al*., 2024). Nevertheless, accumulated data provide a foundation for future developments. First, polygenic risk scores (PRS), which aggregate the effects of many alleles, are being actively investigated and could be used to identify girls at high genetic risk before disease manifestation (Zhu *et al*., 2022; Chen *et al*., 2024; Moolhuijsen *et al*., 2026). Second, identification of key genes (*DENND1A*, *AMH*, *INSR*) opens opportunities for discovering new therapeutic targets. In particular, a multicenter 2025 analysis employing gene-drug screening proposed several potential drugs for repurposing in PCOS (Zhao *et al*., 2023). However, there is broad agreement among authors that large prospective studies are needed before these approaches can be translated into clinical practice (Al Abadie *et al*., 2023; Guzek *et al*., 2023; Ncube *et al*., 2023; Oran & Azer, 2023; Szklener *et al*., 2023; Tam *et al*., 2023; Tsvetkova *et al*., 2023).

Conclusion

The analysis of current literature presented here allows us to state that over the past decade, the understanding of the genetic basis of polycystic ovary syndrome has undergone fundamental changes. From scattered and poorly reproducible candidate gene associations, the research community has moved toward recognizing PCOS as a polygenic disorder in which dozens, and likely hundreds, of genetic loci participate. Each of these loci individually contributes only modestly to risk, yet together they determine the high heritability of the syndrome and explain its clinical heterogeneity.

A key outcome of genome-wide studies has been not merely the identification of specific genes, but the delineation of major pathogenetic nodes: neuroendocrine dysregulation (involving *FSHB*, *FSHR*, *LHCGR*), metabolic disturbances (*INSR*, *THADA*, *HMGA2*), and intraovarian mechanisms of hyperandrogenism (*DENND1A*, *AMH/AMHR2*). These nodes mustn't be isolated – their cross-interaction creates the very continuum of phenotypes observed in clinical practice, ranging from predominantly reproductive forms to pronounced metabolic variants of the syndrome.

Alongside common polymorphisms, rare genetic variants are attracting increasing attention. Although they occur in only a small proportion of patients (5-10%), their study holds particular value because it enables the identification of monogenic and oligogenic subtypes of PCOS, including in women without classical risk

factors (obesity, insulin resistance). These rare variants offer the most direct routes to understanding causal relationships and to discovering new therapeutic targets.

At the same time, even after large-scale multinational GWAS, a substantial portion of PCOS heritability remains unexplained. The contribution of rare variants, epigenetic modifications, gene-environment interactions, and unaccounted types of genetic variation (e.g., structural variants) has yet to be evaluated. This does not diminish what has been achieved, but it sets a direction for future research.

From a practical standpoint, current genetic data have not yet been translated into routine clinical tests or treatment algorithms. Nevertheless, they have already laid a foundation for the development of polygenic risk scores, personalized prediction, and, in the longer term, targeted therapy. With cautious optimism, one can assume that genetic information will eventually complement existing clinical tools for the prevention and treatment of PCOS; however, this will require further large-scale prospective studies integrating genomic, epigenomic, and clinical data.

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