

Review Article

Genetic Markers of Polycystic Ovary Syndrome: Emphasis on Insulin Resistance

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of childbearing age causing not only reproductive but also metabolic anomalies. PCOS women present with ovulatory dysfunction, abnormal hormones, hyperandrogenemia, obesity, and hyperinsulinemia. It is a heterogeneous disorder which results from interaction of multiple genes along with environmental factors. Insulin resistance is a central key element contributing to PCOS pathogenesis and is further aggravated by obesity. Insulin regulates metabolic homeostasis and contributes to ovarian steroidogenesis. Candidate gene analyses have dissected genes related to insulin secretion and action for their association with PCOS susceptibility. Although a large number of genomic variants have been shown to be associated with PCOS, no single candidate gene has emerged as a convincing biomarker thus far. This may be attributed to large amount of heterogeneity observed in this disorder. This review presents an overview of the polymorphisms in genes related to insulin signaling and their association with PCOS and its related traits.

1. Introduction

Polycystic ovary syndrome (PCOS) is the major cause of anovulatory infertility affecting millions of women worldwide. Despite years of research and huge amounts of investment, the etiology of PCOS is still poorly understood [1]. It is typically characterized by chronic anovulation, excess androgen production, and presence of polycystic ovaries on ultrasound. Clinically these women present with irregular menses, hirsutism, acne and alopecia, and elevated LH : FSH ratio along with insulin and androgen excess. This syndrome also confers a greater risk of development of impaired glucose tolerance and subsequent type 2 diabetes mellitus (T2DM), as well as metabolic syndrome and cardiovascular diseases (CVD) in later life [2]. Insulin resistance, the hallmark feature of PCOS and its associated compensatory hyperinsulinemia, is seen in approximately 50–70% of affected women [3]. Central obesity is present in both lean and obese women with PCOS which further aggravates insulin resistance and worsens the aforementioned symptoms in these women [4].

2. Insulin Resistance and PCOS

Insulin which is a potent anabolic hormone controls diverse processes essential for tissue metabolism, growth, and survival. Binding of insulin to its receptor initiates a cascade of signaling events and activates an array of molecules by which insulin exerts its pleiotropic actions. The insulin receptor (INSR) is a membrane bound receptor with intrinsic tyrosine kinase activity. It is capable of binding to insulin and insulin-like growth factor-1 (IGF-1) at the alpha subunits which lead to activation of intrinsic tyrosine kinase activity and phosphorylation of the beta subunits. Activated INSR stimulates a wide array of downstream molecules including the intracellular insulin receptor substrates (IRS1-4), the Shc adapter protein isoforms, signal regulatory protein (SIRP) family members, Gab-1, phosphatidylinositol-3-kinase (PI3K), Akt2, Cbl, and APS. Phosphorylation and stimulation of these molecules play an essential role in GLUT4 translocation to the plasma membrane and glucose uptake. INSR present in lipid raft microdomains of the plasma membrane activates APS proteins and stimulates

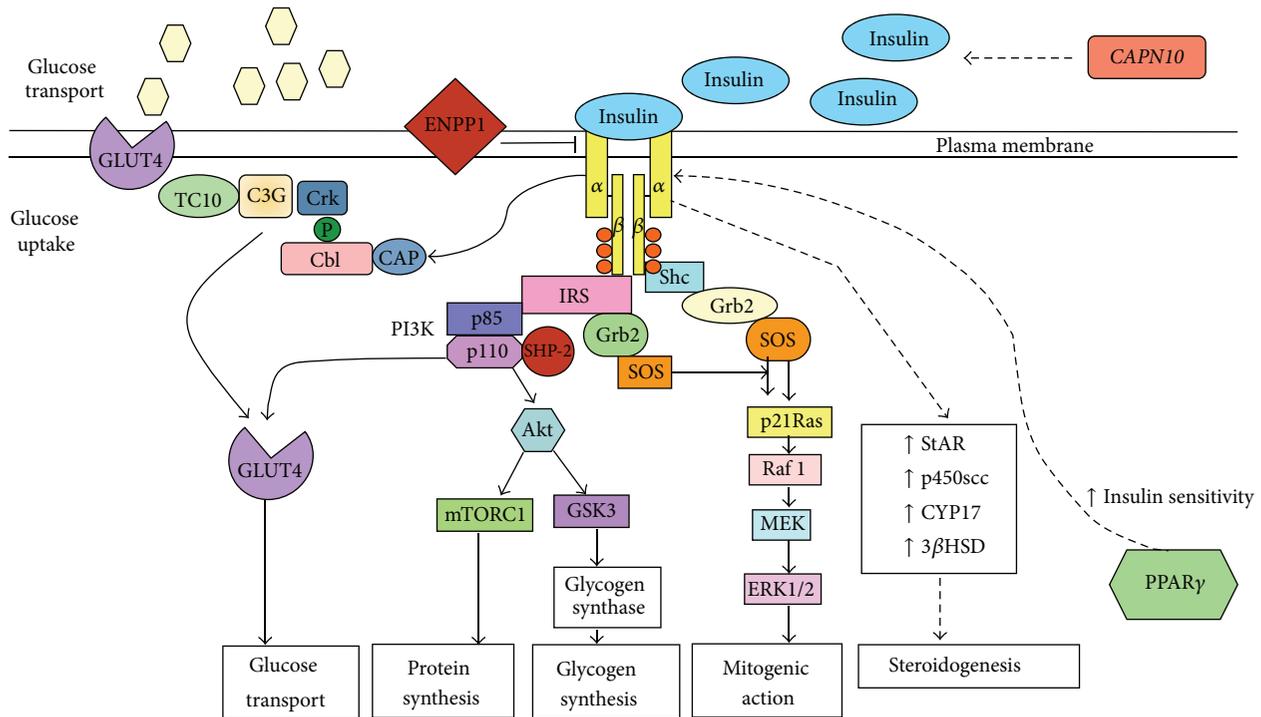


FIGURE 1: Interaction of insulin with insulin receptor (INSR) triggers key molecular signal cascades which participate actively in effecting pleiotropic biological actions in respective target cells. Insulin binding activates INSR β subunit tyrosine kinase which phosphorylates IRS proteins that subsequently activates downstream mediators thus facilitating metabolic and mitogenic actions of insulin. IRS: insulin receptor substrate; Shc: Src homology domain containing transforming protein 2; PI3K: phosphatidylinositol 3-kinase; Grb2/SOS: growth factor receptor-bound receptor 2/Son of Sevenless; MAPK: mitogen-activated protein kinase pathway; PIP3: phosphatidylinositol 3,4,5-triphosphate; SHP-2: SH2 domain containing protein tyrosine phosphatase; Akt: protein kinase B; mTORC1: mammalian target of rapamycin complex 1; GSK3: glycogen synthase kinase 3; GLUT4: glucose transporter type 4; MEK: MAP kinase kinase; ERK1/2: extracellular signal regulated kinase 1/2; StAR: steroidogenic acute regulatory protein; p450scc: P450 side-chain cleavage; CYP17: cytochrome P450c17; 3β HSD: 3β -hydroxysteroid dehydrogenase; CAP: c-Cbl Associated Protein; C3G: Crk SH3-binding guanine nucleotide-releasing factor; ENPP1: ectoenzyme nucleotide pyrophosphate phosphodiesterase; CAPN10: calpain-10; PPAR γ : peroxisome proliferator activated receptor gamma.

tyrosine phosphorylation of protooncogenes c-Cbl and Cbl-b. CAP (c-Cbl Associated Protein) is subsequently phosphorylated and forms the flotillin-CAP-Cbl complex which in turn interacts with the CrkII: C3G complex and localizes to lipid rafts activating TC10 thereby promoting GLUT4 translocation. The mitogenic action of insulin is exerted through binding of phosphorylated IRS1/2 or Shc with Grb-2/SOS complex and subsequent p21Ras and Raf-1 activation of mitogen-activated protein kinase pathway (MAPK) [5, 6]. Insulin thus activates different downstream signaling pathways which facilitates its metabolic and mitogenic actions on respective target cells (Figure 1).

Insulin resistance, defined as the reduced cellular ability to respond to normal or elevated levels of insulin, appears to be an important pathophysiologic mechanism in the development of metabolic disturbances in PCOS. It is now an intrinsic component of PCOS existing in a majority of women irrespective of being lean or obese [7]. A striking phenomenon of presence of hyperinsulinemia in women with PCOS was first reported by Burghen et al., 1980 [8]. Women with PCOS have increased prevalence of glucose intolerance and metabolic syndrome [9]. Insulin resistance could also cause or exacerbate the clinical manifestations of

PCOS, including ovulatory dysfunction, hirsutism, hyperandrogenemia, and metabolic abnormalities [10]. The presence of INSR and IGF-1 receptors in the ovarian cells suggests it is an important target organ for insulin action. Insulin not only exerts metabolic and mitogenic action but also influences steroidogenesis in the ovary by increasing expression of steroidogenic acute regulatory protein (StAR), P450 side-chain cleavage (P450scc), 3β -hydroxysteroid dehydrogenase (3β -HSD), and cytochrome P450c17 (CYP17) [5]. Excess insulin can act as a co-gonadotropin alone or synergistically with LH on ovarian thecal cells to synthesize more androgens [11]. Insulin along with LH may also upregulate intracellular cAMP concentration in theca cells to increase expression of steroidogenic genes, further contributing to excess androgen synthesis. Additionally it also reduces hepatic biosynthesis of sex hormone binding globulin (SHBG) as well as production of IGF binding proteins which regulates the bioavailability of testosterone and IGF-1 levels, respectively. IGF-1 availability further enhances insulin activity contributing to hyperinsulinemia. The molecular mechanism by which insulin enhances androgen synthesis in ovary of women with PCOS despite being insulin resistant is still elusive [5]. Studies undertaken to understand the molecular mechanism

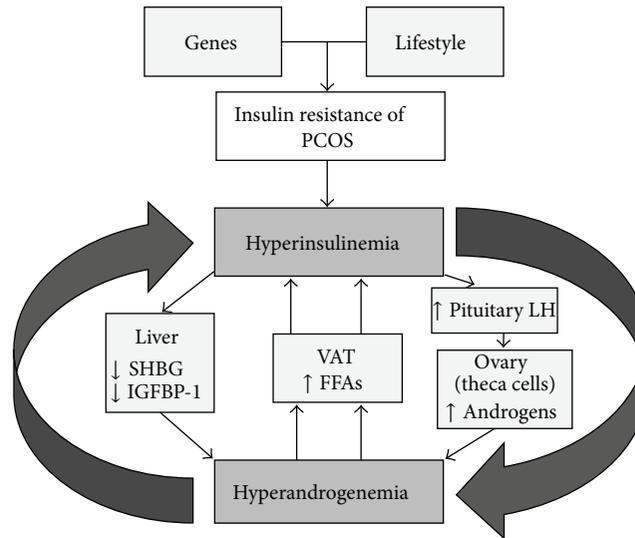


FIGURE 2: The vicious cycle between hyperinsulinemia and hyperandrogenemia underlying PCOS development: compensatory hyperinsulinemia expands the androgen pool by acting directly on the thecal ovarian cells and indirectly by reducing hepatic biosynthesis of SHBG and IGFBP-1. Excess androgens in turn stimulate VAT to generate FFAs which further contributes to insulin resistance. These phenomena work hand in hand to maintain the PCOS state. SHBG: sex hormone binding globulin; IGFBP-1: insulin-like growth factor binding protein 1; VAT: visceral adipose tissue; FFAs: free fatty acids; LH: luteinizing hormone.

of insulin resistance highlighted that 50% of PCOS women demonstrate postreceptor insulin binding defect in skeletal and fibroblast tissues [12]. Increased serine phosphorylation has been associated with decreased INSR tyrosine autophosphorylation thus hampering insulin signaling. This mechanism may be attributed to the presence of an as yet unidentified common serine kinase or absence of serine phosphatase involved in both insulin signaling and androgen synthesis pathways [13]. Increased serine phosphorylation may increase expression of Cyp17A1 and at the same time confer insulin resistance by inactivating INSR as well as by phosphorylating the downstream insulin signaling pathway molecules such as IRS-1 and PI3K at serine residues and subsequently impairing insulin related responses [13]. These findings clearly highlight that insulin contributes to excess androgen production in PCOS ovaries. Excess androgens increase the expression of lipolytic β 3-adrenergic receptors on visceral adipose tissue (VAT) [14] which favors release of free fatty acids (FFA) contributing to insulin resistance and hepatic gluconeogenesis leading to a prediabetes/insulin resistant state [15]. The pathogenesis of PCOS may be looked upon as a vicious cycle involving both hyperinsulinemia and hyperandrogenemia to maintain the PCOS state (Figure 2).

3. Candidate Gene Approach to Elucidate PCOS Pathophysiology

Studies identifying familial clustering of cases have established a genetic basis of PCOS [16]. Evidence suggests it to be a complex heterogeneous syndrome in which both genetic and environmental influences play an important role in its manifestation [17]. In order to elucidate its underlying molecular mechanisms, researchers have investigated candidate genes

to understand the inherited causes of PCOS and its related phenotypes. Several polymorphisms and mutations confer clinical and biological significance in the proper functioning of a gene and its product. A large array of putative candidate genes involved in regulation of insulin secretion and action, ovarian and adrenal steroidogenesis, gonadotropin action and regulation, inflammation, and energy regulation has been studied in relation to PCOS. The present review highlights the influence of polymorphisms of important genes involved in insulin action and regulation and their contribution to PCOS susceptibility and its related traits.

3.1. Insulin (INS). PCOS is likely to show glucose tolerance defect due to abnormalities in insulin secretion and its action. Women with PCOS have pancreatic beta-cell dysfunction and/or decreased hepatic clearance of insulin [18]. The minisatellite variable number of tandem repeats (VNTR) locus on chromosome 11p15.5, located upstream of the insulin gene, regulates its expression. A strong linkage and association between the III/III genotype of *INS* VNTR and anovulatory PCOS was first reported by Waterworth et al., 1997 [19]. Several studies have since looked for association of these VNTRs with PCOS and related phenotypes in different ethnic populations. Vanková et al., 2002 [20], found no association with PCOS or related traits like BMI, insulin, glucose, or c-peptide levels while Ferk et al., 2008 [21], reported a significant association of class III *INS* VNTR alleles with PCOS and obese women with III/III *INS* VNTR genotype showed elevated insulin levels. Similar associations with PCOS were not observed in Finnish [22], Croatian [23], Korean [24], and Han Chinese [25] populations. Recent meta-analysis confirmed a strong association of *INS* VNTR polymorphism with PCOS risk only in anovulatory women

but not with the overall women with PCOS which may explain the contradictory results mentioned above [26].

3.2. INSR. The prime action of insulin is mediated by its receptor INSR, a heterotetrameric protein consisting of two extracellular α subunits harboring the ligand binding domain and two transmembrane β subunits with intrinsic tyrosine kinase domain. The binding of insulin to α subunit of the INSR activates the tyrosine kinase activity of the receptor, triggering the signaling cascades. Impaired sensitivity to insulin is also a common feature observed in women with PCOS. The postbinding signaling defects of INSR have been reported in skeletal muscles and adipose tissues of women with PCOS. Linkage based studies have identified D19S884, a microsatellite marker on chromosome 19 p13.2 lying in close vicinity to *INSR* gene having strong association with PCOS [16]. This was further confirmed in a case control study by Tucci et al., 2001 [27], in Caucasian women with PCOS and Xie et al., 2013 [28], in Han Chinese population. However a study with Caucasian women from Spain and Italy failed to show such association [29]. The most widely studied polymorphism in *INSR*, the C/T His1058His (*rs1799817*) polymorphism which lies in exon 17, encoding partially the tyrosine kinase domain of INSR was investigated for its association in many populations. This polymorphism showed significant association with lean women with PCOS in Caucasian [30], Chinese [31], Indian [7], and Japanese [32] populations. Except for the Japanese study, the frequency of polymorphic (CT+TT) genotype was higher in lean PCOS subjects according to BMI stratification. In our study with Indian women, we found the same polymorphism to be associated with PCOS but only in lean women. Further this showed association with hyperinsulinemia and hyperandrogenemia in the same lean subgroup. Our study further strengthens the concept that insulin resistance pathogenesis could vary among different subgroups of women with PCOS on the basis of BMI classification [7]. However the same His 1058 C/T SNP showed no association with PCOS in Korean [33], Iranian [34, 35], and Croatian population [23]. A meta-analysis reported no association of His1058 C/T SNP with PCOS but warranted further studies to confirm this finding [36]. A novel polymorphism *rs176477* C/T in exon 17 was identified to be associated with PCOS in Korean population [37]. Goodarzi et al., 2011, using tag-SNP approach, observed the association of four novel SNPs with PCOS in Caucasians; however, in a replicative cohort, association of only one SNP (*rs2252673*) was persistent [38]. From these studies, *INSR* gene surely stands as an important candidate gene having influence on PCOS and its insulin resistance component.

3.3. IRS. Phosphorylated IRS enables activated INSR to communicate with downstream mediators of insulin signaling, including PI3K, Fyn, Grb-2, and Crk [39]. After insulin stimulation, IRS-1 associated PI3K activity was decreased in PCOS skeletal muscle but no difference was detected in fibroblasts of PCOS women [40] when compared to controls. On the other hand, theca cells from PCOS women express increased IRS-1 and IRS-2 and decreased IRS-4 levels, while

no changes were observed in IRS-1, -2, or -4 levels in the granulosa cells. These findings may explain the amplification of ovarian insulin sensitivity with increased theca cell proliferation and consequent ovarian hyperandrogenism seen in these women [39]. Studies have been dedicated to examine the effect of two common polymorphisms in *IRS-1* (Gly972Arg) and *IRS-2* (Gly1057Asp) with PCOS predisposition and its associated phenotypes. Gly972Arg polymorphism of *IRS-1* reduces its phosphorylation and allows IRS-1 to act as an inhibitor of the INSR kinase, thereby impairing insulin signaling [41]. This polymorphism has shown significant association with PCOS in Italian [42], Greek [43], Japanese [44], and Turkish [45] women. Contradictory results of no association have been reported in studies with Greek [46], Slovak [47], South Chilean [48], Taiwanese [49], Spanish [50], German [51], South Indian [52], Caucasian [53], and Croatian [23] women with PCOS. On the other hand, *IRS-2* polymorphism revealed no significant association with PCOS [43, 51] but has been related to glucose dysmetabolism in these women [53, 54]. A Mendelian meta-analysis has confirmed significant association of *IRS-1* (Gly972Arg) polymorphism with the risk of developing PCOS and impaired insulin signaling [36]. A recent meta-analysis also revealed significant association of *IRS-1* Gly972Arg polymorphism with PCOS but not with *IRS-2* Gly1057Asp polymorphism [55].

3.4. ENPPI. The ectonucleotide pyrophosphate/phosphodiesterase (ENPPI) also known as plasma cell membrane glycoprotein (PC-1) is a class II membrane glycoprotein that effectively binds the INSR. Binding induces conformational changes that lead to its reduced tyrosine kinase activation and autophosphorylation, thereby inhibiting insulin signaling [56]. A gene expression study carried out by Corton et al., 2007, in omental adipose tissue from PCOS women showed overexpression of ENPPI emphasizing the significance of ENPPI in contributing to insulin resistance [57]. A functional missense polymorphism (*rs1044498*) in exon 4 causes an amino acid change from lysine to glutamine (K121Q). The Q variant interacts more strongly with the INSR than the K variant and reduces INSR autophosphorylation [56]. A study in Finnish women strongly implicates the role of this polymorphism in PCOS susceptibility [58]. However subsequent studies in Spanish [59], Japanese [44], and Saudi [60] women demonstrated no association with PCOS and its related metabolic or hormonal traits.

3.5. Calpain-10. Calpain-10 is a ubiquitous calcium dependent serine protease which actively participates in cellular signaling, insulin secretion and action, and differentiation of preadipocytes into adipocytes [61]. Calpain inhibition is associated with increased glucose-induced insulin secretion in pancreatic islets but decreased insulin-stimulated glucose uptake in muscle and adipocytes and decreased muscle glycogen synthesis [62]. Calpain-10 was identified as a candidate gene for T2DM by positional cloning and its genetic variants have been shown to be associated with elevated FFA and insulin resistance [61]. The contribution of *CAPN10* polymorphisms (UCSNP-44, -56, -43, -19, and -63) to PCOS pathogenesis and typical traits has yielded conflicting results

with some studies indicating no association at all [34, 63]. The risk of development of PCOS was increased 2-fold in both Caucasian and African American women with *CAPN10* 112/121 haplotype. Further this haplotype also showed association with increased insulin levels in African-American women with PCOS [64]. The UCSNP-44 has been found to be associated with increased PCOS risk in Indian [65], Turkish [66], and Spanish [67] populations as well as with indices of hyperandrogenemia and hyperinsulinemia [66, 67] in afflicted women. Studies have also confirmed association of UCSNP-43 with PCOS as well as metabolic syndrome in PCOS [68, 69]. A study with German women observed a significant association of UCSNP-19 ins/del and UCSNP-56 with PCOS among the eight variants they studied [70] of which UCSNP-56 was not replicated in Chinese women [71]. Specific haplotypes and diplotypes have been found to be associated with increased or decreased PCOS susceptibility in Korean women with PCOS [72]. Recently a meta-analysis indicated association of UCSNP-19/-63/-45 polymorphisms with PCOS risks with ethnic specific differences [73]. Another meta-analysis revealed that homozygous carriers of UCSNP-63 and insert allele of UCSNP-19 serve as protective factors for PCOS while the heterozygous genotype and deletion allele of UCSNP-19 posed higher risk for PCOS susceptibility [74].

3.6. *PPAR γ* . Peroxisome proliferator activated receptor gamma (*PPAR γ*) is an important nuclear transcription factor involved in regulating glucose and lipid metabolism and also ovarian steroidogenesis [75]. It is an important adipocyte differentiator which regulates energy balance and enhances insulin sensitivity [76]. The most widely studied genetic polymorphism is the proline (Pro) to alanine (Ala) variant at codon 12 in exon B of *PPAR γ* . The Ala variant of *PPAR γ* has been associated with decreased receptor transactivation, lower BMI, and increased insulin sensitivity [77]. Several studies have evaluated the association of this variant with PCOS risk as well as obesity and insulin resistance parameters with positive and negative results. Increased insulin sensitivity, decreased fasting insulin levels, HOMA-IR, and basal metabolic rate were observed in women with PCOS who were carriers of Ala alleles [78–81]. There was significantly reduced tendency of Ala allele occurrence in PCOS group as compared to the control group and this showed association with PCOS in Indian, Finnish, Turkish, and Korean populations [78, 79, 82, 83]. In our study with Indian women we observed that carriers of polymorphic Pro12Ala (CG+GG) genotype had significantly lower 2 hr glucose levels [82]. A recent study also demonstrated that Pro12Ala was significantly associated with insulin sensitivity in lean PCOS women of Croatian population [84]. On the contrary, studies in German, Chinese, Caucasian, and Greek population showed no association of this polymorphism with PCOS [81, 85–90]. A meta-analysis indicated Ala alleles reduce the probability of having PCOS in European populations but not in Asians, which included only Chinese and Korean studies [91, 92]. Another polymorphism in *PPAR γ* gene, His 447His (C1431T) in exon 6, is reported to be frequent in PCOS women. This variant has shown association with PCOS [52, 83, 93], obesity and higher leptin levels [93],

and decreased testosterone levels [89] in affected women. We observed association of this variant with lower insulin, HOMA-IR, and 2 hr glucose levels in women with PCOS [82]. However Antoine et al. showed association of this SNP with reduced levels of testosterone, insulin, and decreased insulin resistance in normal healthy women [87]. Our study showed that PCOS women with polymorphic Pro12Ala genotype were better protected against development of PCOS and carriers of both polymorphic genotypes had better insulin sensitivity and improved glucose metabolism suggesting variations in *PPAR γ* gene influence the insulin resistance pathophysiology in Indian women with PCOS [82]. Overall these association studies imply *PPAR γ* to be an important gene associated with PCOS and its related traits.

4. Genome Wide Association Studies (GWAS): New Avenues in PCOS Research

GWAS are now at the forefront of genetic technologies which have shed light on the biological pathways underlying complex disorders [94]. These studies offer an advantage at controlling population stratification, hypothesis generation, and detection of novel susceptibility loci [95]. This upcoming field has generated a wide database of SNPs following the completion of the Human Genome Project as well as the HapMap project which has helped to dissect the genetic architecture underlying many disease states. Till date, few GWAS studies have been published in the field of PCOS. A two-stage GWAS was first undertaken by Chen's group, an initial discovery set for GWAS and the second stage of the replication study which included two independent cohorts from northern Han Chinese and from southern and central Han Chinese. Their study has identified three novel PCOS susceptibility loci, namely, 2p16.3, 2p21, and 9q33.3, which mapped to the genomic areas of three genes *LHCGR*, *THADA*, and *DENNDIA*, respectively [96]. A second GWAS study in a larger sample of Han Chinese women confirmed the previously identified loci and revealed association of eight new loci which correspond to genomic regions involved in insulin signaling, hormonal functions, folliculogenesis, and T2DM associated genes in addition to calcium signaling and endocytosis [97]. Another study explored genotype-phenotype correlations of these susceptibility loci in a large cohort of Han Chinese women and observed that these variants were not only involved in PCOS development but also associated with hormonal and metabolic disturbances in women with PCOS [98]. A third GWAS study performed in Korean population identified *GYS2* to be significantly associated only with the obese subgroup of PCOS women [99]. Given that ethnicity influences the phenotypic diversity in PCOS, Louwers' group studied cross-ethnic effects of the loci identified in Chinese women with PCOS, in women of Northern European descent, and concluded that there existed a common genetic risk profile for PCOS across these populations [100]. Further resequencing and fine-mapping of the loci identified in Chinese GWAS studies were carried out to verify associations in Caucasian populations with PCOS. Subsequent replication studies have confirmed the association of *DENNDIA* variants with PCOS susceptibility as well

as with hyperandrogenism and unfavorable lipid profiles in affected women [101–104]. While the GWAS discoveries must be confirmed by candidate gene based replication studies in various ethnic populations, there is no denying that this fast paced field offers immense potential to pinpoint genes which identify biological processes involved in etiology of multi-dimensional polygenic disorders like PCOS.

5. Conclusion

PCOS is a multifaceted disorder whose consequences extend beyond the reproductive axis and which has a major effect throughout life on the reproductive, metabolic, and cardiovascular health of affected women. The exact etiology of this multigenic and multifactorial disorder remains elusive even today despite rigorous efforts. This review has summarized the role of putative genetic variants contributing to the insulin resistance state frequently observed in PCOS women. Several pathways interlinking metabolic and reproductive processes have been dissected by studies aimed at understanding the genetic origin of this disorder. With the purpose of delineating genetic predisposition factors involved in PCOS susceptibility and prognosis related with insulin resistance, researchers have embarked upon a long journey to detect essential gene variants which are critical to PCOS pathophysiology. However, in spite of immense effort, inconclusive data has been generated due to lack of uniformity in diagnosis criteria, small sample size, ethnic variation, environmental factors, heterogeneous population, and so forth. Nevertheless an amalgamation of these studies has divulged several plausible genetic loci with high priority candidate genes and a number of future studies would be advantageous in selecting the appropriate genes as biomarkers. As insulin resistance enhances hyperandrogenemia as well as metabolic dysfunctions in PCOS, identification of candidate genes can help to assign predisposition factors and establish genetic makeup of affected women. This would further help to understand complex phenotypes of PCOS and advance the design of therapeutic approaches which would ameliorate major comorbidities like T2DM, metabolic syndrome, CVD, endometrial cancer, and so forth in later life.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Nuzhat Shaikh and Roshan Dadachanji equally contributed to drafting the paper. Srabani Mukherjee provided overall guidance and editorial assistance.

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