Original Article

Contemporary Knowledge on the Genetic Basis of Polycystic Ovarian Syndrome

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Polycystic Ovarian Syndrome (PCOS) is a reproductive disorder commonly found in adolescent and young women. It is a leading cause of female infertility. So, considerable attention should be given to explore its cause and mechanism. Primarily, scientists noted that several environmental and lifestyle related factors like lack of physical activity and overeating lead to insulin resistance, hyperinsulinemia and finally to PCOS. In addition, some extraovarian factors like different cytokines, biomolecules, heat shock proteins and oxidative stress were found to be involved in the disease process. But all of these are external causes. If we want to go deeper to extend the causal chain, we should set out on a journey to the genetic domain. In the meanwhile, scientists picked up a valuable clue. They observed that PCOS runs in families and is more prevalent in specific ethnic groups. This observation supplied an indication of possible chromosomal or genetic link behind this syndrome. Now, the trip began and after a lot of research they determined that a single chromosomal site or gene cannot be blamed rather multiple genes and their cross-talk is responsible behind this complex process. Further analysis revealed that, in fact, 241 gene variation might be involved in the dynamics. Present article is a faithful representation of this historic journey in a lucid yet scientifically rigorous manner. Authors conclude that further intensive, careful and elaborate research is necessary in this direction to discover the genetic links behind the entire system and process of the globally uprising problem.

[*J Indian Med Assoc* 2023; **121(9):** 54-9]

Key words **: Polycystic Ovarian Syndrome (PCOS), Genetics, Epigenetics.**

Polycystic Ovarian Syndrome (PCOS) is a multifactorial endocrine reproductive disorder common among a large population of women across the globe. It is also seen to run in families and found to be more prevalent amongst specific ethnic groups. Several studies have already been directed to find specific chromosomal or genetic clues behind causation of this syndrome. Some of them are very optimizing, but none is conclusively indicative of a single chromosomal site or gene. This narrative review is intended to extensively surf the possible factors behind the causation and/or phenotypic expression of this widely prevalent syndrome.

Clinical Manifestations :

PCOS usually presents in adolescent and young adults with variety of manifestations, like Oligo/ Amenorrhea, Obesity, Acne, Hirsutism, Hypertension, Impaired Glucose Tolerance, Type-2 Diabetes Mellitus (T_2DM), etc, in various combinations[1]. There remains no consensus of diagnostic criteria of the syndrome. NIH Criteria (1990) – long standing anovulation, hyperandrogenism; Rotterdam Criteria (2003) – any two of oligo or anovulation, clinical or biochemical hyperandrogenaemia, Ultrasound features of Polycystic ovary; and AE-PCOS Society Criteria (2006) – biochemical and clinical evidence of hyperandrogenism, dysfunction ovaries, polycystic ovary morphology, are the three major criteria for diagnosis of PCOS[2]. Diagnostic workup includes evaluation of androgen level, LH, FSH and serum prolactin levels, SHBG level, fasting and postprandial glucose, clinical evaluation of hirsutism by modified Ferriman-Gallwey Score and ultrasonic evaluation of number of antral follicles and ovarian volume; and second-line investigations include estimation of Anti-

Editor's Comment :

- Despite extensive genetic research, no specific genes have been identified as related to the aetiopathogenesis of PCOS.
- Other types of omics studies, such as transcriptomics, epigenomics, proteomics, metabolomics, etc, have also not provided specific insights into the underlying causes of PCOS.
- It is crucial to intensify and expand research efforts to understand the origin, development, prevention, and treatment of PCOS, possibly leading to a more appropriate naming of the condition.

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Received on : 20/08/2022
Accepted on : 11/07/2023

mullerian Hormone (AMH), androgen levels and lipid profile (Homburg, *et al,* 2013; Lam *et al*, 2006).

Over the time it has been differently termed as Sclerocystic ovaries, Multicystic ovaries, Stein Leventhal syndrome, etc[3]. But Teede H, *et al*, 2013 and Khadilkar SS, 2016 raised some controversies regarding the appropriateness of globally-used terminology, Polycystic Ovarian Syndrome (PCOS).

PCOS is related to upto 40% of female infertility[4]; and is a leading cause of endometrial carcinoma[5]. Insulin-resistance in PCOS leads to not only glucose intolerance, T_2DM and Hypertension, but also dyslipidemia, hepatic steatosis and cardiovascular morbidities[6]. Overall global prevalence among female under 18-44 age group is 5-15% (Teede, *et al,* 2010; Ricardo, 2016). Following NIH Criteria, prevalence of PCOS in Caucasian and black races were around 4%, (Knochenhauer *et al,* 1998) but in another study it was found to be 8% in white and 4% in black races[7]. Among Greek women, it was 6.8%, and so among Spanish Caucasians also (Asunción, *et al 2000*), Among Chinese women of reproductive age group, it is 5.6%, (Li, *et al,* 2013) but among similar cohort of Indian women, it is nearly 9.13% (Nidhi, *et al,* 2011). Using Rotterdam Criteria, a study in Pakistan reported about 50% prevalence rate (Aqram, *et al,* 2015) and in another study it was 40% using the same criteria in Pakistan (Baqai, *et al,* 2010).

Not ovarian morphology but hyperandrogenism, Body Mass Index (BMI) and menstrual irregularities predict metabolic dysfunction in PCOS[8,9]. Considering all the common criteria – Ultrasonographic Ovarian Morphology, Oligo/Anovulation and Hyperandrogenism, Khan, *et al* (2019) classified PCOS into four phenotypes – A, B, C and D, as follows[10-12] (Table 1) :

Table 1 — *Phenotypic Classification of PCOS (consolidated)*

Phenotype	Clinical Criteria			Prevalence
	Polycystic Ovarian Morphology in USG	Oligo/ Anovulation	Hyperandrogenism	
A	Y	Y	Y	44-65%
B	N	Y	Y	8-33%
C	Y	N	Y	3-29%
D	Y	Y	N	0-23%

In short, phenotype A and B belong to classic PCOS, phenotype C to ovulatory PCOS and phenotype D to non-hyperandrogenic PCOS. Classic PCOS (phenotypes A and B) were related to hyperinsulinemia, insulin-resistance, Metabolic Syndrome, Obesity, Atherogenic Dyslipidemia[13], Hepatic Steatosis[14] and significantly elevated level of AMH[15]. Ovulatory PCOS (phenotype C) with normal routine menses, besides having high score Hirsutism, they were having mild degree of insulin resistance, atherogenic dyslipidemia and metabolic syndrome, which might be due to excessive diet and physical inactivity among the high Socio-economic group in which these phenotypes were more prevalent[11,16]. Non-hyperandrogenic PCOS (phenotype D), had regular menses with intermittent irregularities[17], showing elevated SHBG with normal androgen level and low T3, T4, FSH and LH levels[18], as well as least metabolic dysfunction[19,20].

But this classification was not agreed by many investigators as they found wide variation of PCOS phenotypes. In Germans, different PCOS phenotypes were found but with no significant variation in BMI, IR and Dyslipidemia[21]. In Greeks, similar metabolic alterations were found only in PCOS women with more than 25 kg/m^2 BMI[22]. In Sri Lanka and Brazil also, significant variation in metabolic syndrome were not observed among PCOS women (Wijeyaratne, *et al,* 2011; Melo, *et al,* 2011. In Turkish PCOS cohort, elevated LDL levels were found in phenotype C group with respect to phenotype D group as above (Ates, *et al,* 2013). Some investigators were also doubtful regarding the method of androgen estimation across the globe (Rosner, *et al,* 2007). The three standard diagnostic criteria, as described before, accepted different phenotypes in their categorization, eg, phenotype A and B by NIH, all four by Rotterdam Consensus and phenotypes A, B and C by AES-PCOS[23,24].

Etiology of PCOS :

PCOS is a multifactorial syndromic disorder involving both genetic and environmental interplay. Franks, *et al* defined PCOS as ovarian pathology of androgenic overproduction and heterogenous manifestations according to interplay of genetic predisposition –determining the ovarian pathology – with other genetic and environmental factors (Franks, *et al,* 2006).

According to database, 241 gene variation might be involved in its etiology (Joseph, *et al,* 2015). A defect in the transcriptional activity of a gene leading to PCOS might be due to polymorphism or any nucleotide change. Genes encoding for androgen receptors, LH receptors, FSH receptors and leptin receptors are mostly considered to be responsible for these[25]. PCOS were considered to be related to polymorphisms of StAR, FSHR, FTO, VDR, IR and IRS, GnRHR[26]. Progression and severity of PCOS was found to be related to hyperinsulinemia and hyperandrogenemia. Hyperinsulinemia acting over the ovarian theca cells

raise androgen level and reduce hepatic biosynthesis of SHBG and IGFBP-1. Again, Androgen level stimulating Visceral Adipose Tissue (VAT) increases Free Fatty Acid (FFA) leading to IR, thus a vicious cycle actually escalates the etiopathogenesis of PCOS[2]. 5α-reductase in the theca cell increased 5α-androstane-3,17-dione concentration and inhibited the activity of aromatase in granulosa cells. In PCOS, LH and progesterone acting over the granulosa cells yielded high androgen level and low Estrogen level (Denis, 2006). But the intrauterine Androgen excess was considered to be fetal, not maternal, as the fetus got protected by placental aromatase activity and high maternal SHBG concentration[1]. Usually quiescent fetal ovary, in subjects genetically pre-disposed to PCOS,could produce excess androgen under influence of maternal HCG[1].

Some investigators suggested a cross-generational relationship between the degree of maternal hyperandrogenism and development of PCOS in their daughter during adolescence, particularly when the HPO axis got activated[1]. Gestational hyperglycemia, *vis-a-vis* fetal hyperinsulinemia, might be accompanied by mid-gestational androgen excess in female fetuses; and excess amount of mid-gestational maternal Testosterone level could predict high AMH levels in their daughter during adolescence (Hart, *et al,* 2010).

Physiological excess of insulin level and reduction of SHBG level during puberty could escalate the effect of hyperandrogenemia; and physiological hyperinsulinemia directly could stimulate ovarian steroidogenesis, hyperandrogenism and anovulation. Overweight girls pre-disposed to insulin resistance were found to be more susceptible for developing early adrenarche and PCOS in adolescence (Lewy, *et al,* 2001). Hyperandrogenemia in obese pre-pubertal girls were found to have frequent low amplitude LH surges, thus causing reduced inhibition of GnRH pulse frequency by progesterone and increase in Ovarian androgen production by rapid LH pulses (Rosenfield, *et al,* 2010; Burt, *et al,* 2010; Blank, *et al,* 2009).

Epigenetics of PCOS :

Epigenetic factors were found to be significantly related to the etiopathogenesis of PCOS. Influences of different epigenetic factors were considered to attribute even from the womb among female fetuses genetically pre-disposed to PCOS. Subsequent lifestyle pattern, like paucity of physical activity and overeating in girl child also led to insulin resistance, hyperinsulinemia and its sequelae resulting in development of PCOS. Hyperandrogenic exposure *in utero* epigenetically reprogrammed fetal reproductive tissue, which ultimately got translated into PCOS phenotype in later life. Such epigenetic alteration might even persist in germ cell line leading to transgenerational transmission of PCOS[11].

Adverse *in utero* hormonal milieu which could lead to SGA (small for gestational age) neonates and subsequent insulin-resistance could epigenetically promotegenetic makeup predisposed to PCOS to manifest as PCOS in adolescence (Moghetti, *et al,* 1996).

Genetics of PCOS :

Though there are several studies indicating genetic pre-disposition to PCOS, yet the matter is not so clearly discernable. Not only are there difference in genetic basis of PCOS between families but also genetic susceptibility of different genes is found to be different in patient from the same family cohort (Goodarzi, *et al,* 2011). Thus, genetic screening to search for a candidate gene in PCOS is not that realistic as even linkage analysis in family cohorts also gives negative results. Parental analysis is also not practical, although there remains few known risk factors only large population-based case-control studies and Genome-wide Association Studies (GWAS) could be of some help in seeking for possible association. Multiple gene mutation was reported from different families, but low or no true penetrance of single gene mutation has as yet been reported. Considering such diverse findings, PCOS turns out to be polygenic and multifactorial systemic disorder involving all genes or mutations that could affect ovaries in direct/indirect ways.

Although it was initially thought by some researcher that PCOS is an autosomal dominant disorder involving a single gene allele, subsequently most of the researchers postulated it to be a polygenic disorder considering the candidate gene either related to androgen synthesis or insulin-resistance or both, along with a long list of possible genes involving different systems of the body of PCOS patients. Intensive study involving women with Chinese or European ancestry indicated allelic variance of fibrillin-3 (FBN3), (Chen, *et al,* 2011; Goodarzi, *et al,* 2012; Welt, *et al,* 2012; Xie, *et al,* 2013) and variance of luteinising hormone receptor (LHR) (Chen, *et al,* 2011; Capalbo, *et al,* 2012; Mutharasan, *et al,* 2013) FBN3 encoding for extracellular matrix protein regulates Transforming Growth Factor (TGF) signaling particularly during early to mid-gestation in the ovary and many other organs and tissues. A8, its allelic variant in PCOS, manifests a metabolically distinct phenotype including insulin resistance (Urbanek, *et al,* 2007, Hatzirodos, *et al*;

2011, Sabatier *et al,* 2011). During this early and mid-gestational period, testosterone exposure induces altered DNA methylation of TGF-β – regulating genes, and subsequently results in PCOS-like traits (Xu, *et al,* 2011). LHR variants might alter LH stimulation of adipogenesis (Dos Santos, *et al,* 2007), leading to further insulin-resistance and hyperandrogenemia perpetuating the etiopathogenesis of PCOS[1].

Extensive studies in search of all possible gene and mutations affecting ovary, either directly or indirectly in association to PCOS, proposed series of genes in some functional groups like ovarian and adrenal steroidogenesis, steroid hormone effect, gonadotrophin action and regulation, insulin action and secretion and few others (Table 2).

Table 2 — *Proposed Series of Genes in Some Functional Groups Associated with PCOS*

Genes related to	Genes
Steroid Synthesis of Ovary and Adrenal Gland	CYP11A1 (chromosome 15q24.1), CYP11B2 (chromosome 8q24.3), CYP17A1 (chromosome 10q24.32), CYP19A1 (chromosome 15q21.2), CYP1A1 (chromosome 15q24.1), CYP21A2 (chromosome 6p21.33), CYP3A7 (chromosome 7q22.1), Cytochrome P450
Steroid Hormone Effects	AR gene & SHBG gene
Gonadotrophin Action and Release	
1. LH & LHR	β-subunit of LH gene
2. AMH	AMH gene (chromosome 19q13.3)
3. FSHR	FSHR gene
Insulin Action and Secretion	INS, INSR, IRSP & CPAN 10
Others	FTO, PCOS1, SRD5A1 & SRD5A2

Genes related to Steroid Synthesis of Ovary and Adrenal Gland :

Of all the steroidogenic enzymes, aromatase, which converts androgen to estrogen, is of paramount importance in physiologic development of HPO axis and normal female phenotypes. Alteration related to this particular enzyme, right from fetal to pubertal age, might result in various PCOS phenotypes. Aromatase deficiency leads to altered ovarian function and hyperandrogenemia, following low or no alteration of C19 to C18. Any abnormality in cytochrome P450 increases risk in PCOS progression through alteration in either single or multiple genes, like CYP11A1 (chromosome 15q24.1), CYP11B2 (chromosome 8q24.3), CYP17A1 (chromosome 10q24.32), CYP19A1 (chromosome 15q21.2), CYP1A1 (chromosome 15q24.1), CYP21A2 (chromosome 6p21.33), CYP3A7 (chromosome 7q22.1)[2].

Genes related to Steroid Hormone Effects :

Androgen Receptor (AR) gene and Sex Hormone-Binding Globulin (SHBG) gene are the principle genes related to PCOS. AR gene allele is on chromosome Xq1, alteration of which, as assessed by GWAS, was reported to be related in causation of PCOS (Urbanek, 2007, Urbanek, 2014) SHBG gene, located on chromosome 17P13-P12, promotes synthesis of SHBG by hepatocytes under control of androgens, insulin and few other metabolic factors (Edmunds, *et al;* 1990, Nestler, *et al,* 1991; Plymate, *et al,* 1998). Variant of SHBG gene and loss of function of this gene due to inhibitory effect of hyperinsulinemia reduce the level of SHBG (Nestler, *et al,* 1991), Single nucleotide polymorphism in the SHBG gene was found to be significantly associated with PCOS (Wickham, *et al,* 2011; Chen, *et al,* 2010.

Genes related to Gonadotrophin Action and Release :

Luteinising Hormone (LH) and its LH Receptor (LHR) gene, Anti-mullerian Hormone (AMH) gene, and FSH Receptor (FSHR) gene are the three major candidates in this group.

(1) Genes for LH and LHR :

Elevated LH increases androgen concentration directly as described earlier; and also, indirectly by decreasing FSH level though negative feedback control and thus limiting androgen to oestrogen conversion (Pigny, *et al,* 2003; Nardo, *et al,* 2008). A point mutation (Trp8Arg and Ile15Thr) was reported in cases with PCOS in a gene encoding the β-subunit of LH. (Furui, *et al,* 1994); although similar mutation was reported in 15% of normal population (Nilsson, *et al,* 1997). Polymorphism of the same gene was also noted in association with PCOS (Roy, *et al,* 1996).

(2) Gene for AMH :

AMH gene (chromosome 19q13.3) encodes AMH that was involved in infertility, and variation of this gene as assessed by whole exon sequencing and GWAS was found to be associated with PCOS (Cate, *et al*; 1986, Gorsic, *et al,* 2017).

(3) Gene for FSHR :

Disruption of FSHR, a GPCR, is associated with abnormalities in gonadal development and hormonal imbalance related to PCOS. Polymorphism of FSHR gene, located on the petty arm of chromosome 2, were noted in higher frequency in PCOS patients than healthy individuals in a study in North Iraq (Gromoll, *et al*, 2005, Baban, *et al,* 2018).

Genes related to Insulin Action and Secretion :

Genes for the Insulin, Insulin Receptor (INSR), Insulin Receptor Substrate (IRS) proteins and Calpain 10 (CPAN 10) gene are the candidate genes considered to be associated with PCOS.

(1) The Insulin Gene :

Insulin acts on theca cell to increase androgen synthesis physiologically at pre-pubertal age (Nardo, *et al,* 2008). This action of insulin is further provoked in PCOS to phospoinositide 3-kinase / protein kinase B pathway (Munir, *et al,* 2004). INS is a sandwich gene (11p15.5) between tyrosine hydroxylase and insulin growth factor – II (IGF-II) (Akram, *et al,* 2015). Transcriptional rate of INS and IGF-II is regulated by VNTR polymorphism at the 5' untranslated region (Paquette, *et al,* 1998), which is associated with PCOS (Waterworth, *et al,* 1997).

(2) INSR Gene :

INSR is similar to turmeric protein with a pair of α and β chains, and both are encoded by the same gene. INS gene is located at chromosome 19p13.2, a larger part of which was extensively searched and D19S884 was only reported to have strongest association with PCOS[27]. Except for this finding, no other association was detected between PCOS and INSR (Sorbara, *et al,* 1994; Kashima, *et al,* 2013; Diamanti-Kandarakis, *et al,* 2006).

(3) IRSP Gene :

High frequency association of Arg972 IRS-1 was reported in women with PCOS by Petermann, *et al*, and much higher frequency of Gly972Arg in IRS-1 was reported in Turkish women with PCOS in Dilek, *et al.* On the other hand, El Mkadem, *et al* reported no such association of significance. Such varied results of association and no association could only be due to environmental and ethnic contribution[10].

(4) CPAN 10 Gene :

CPAN 10 gene, located on the long arm of chromosome-2, encodes a heterodimeric protein, calcium-dependent cysteine protease, and also associated with T1DM (Sáez, *et al,* 2008). The protein calpain 10 impedes insulin secretion and metabolism. Mutation in CPAN 10 is related to PCOS.

Other Genes related to PCOS:

(1) Fat Mass Obesity (FTO) Gene :

FTO gene, located on chromosome 6q, encodes α-ketoglutarase and is reported to be associated with obesity and T_2DM (Wojciechowski, *et al,* 2012). Single Nucleotide Polymorphism, SNP, rs9939609 was significantly associated in PCOS as reported in a study on Pakistani women[28].

(2) PCOS1 Gene :

PCOS1 gene or PCO gene, located on 19p13.2, was initially identified in 2 siblings in 1971, and was ascribed as a susceptible region for PCOS. Urbanck, *et al.* (2005) replicated this study[27].

(3) SRD5A2 and SRD5A1 Genes :

Jakimiuk, *et al* (1999) first reported increased SRD5A activity among women with PCOS. Subsequently, in 2006, SRD5A1 variants were found to be related to increased risk of hirsutism and PCOS, but variant of SRD5A2 was found to have protective role against PCOS[29].

Conclusion

PCOS is a multifactorial syndromic disorder involving multiple organ system, endocrine and metabolic pathways. There are a number of factors, like environmental, epigenetic – right from the mother's womb to the lifestyle of the affected person. Extra-ovarian factors, different cytokines, several biomolecules, heat shock proteins, oxidative stress are also considered to be related to etiopathogenesis of PCOS. Genetic factors are also considered to be very significant in its causation and manifestation. There were extensive studies on several fields to find out the candidate gene or factor but nothing conclusive has yet been there. More intensive studies in regard to the genetic field are imperative. Further discussions on the other factors are also necessary.

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