PCOS – Have we unravelled the genetics?

INTRODUCTION

Polycystic ovary is a heterogeneous condition occurring in the reproductive age group causing metabolic and endocrine imbalance. This leads to clinical manifestations like irregular periods, acne, hirsutism, alopecia, fertility issues and metabolic problems like diabetes and dyslipidemia. The finding of variability in incidence and severity of these clinical manifestations has divided PCOS into various phenotypes. As a result of this, over time the criterion for defining PCOS has changed. The latest NIH guidelines (2018), maintained two out of three initial criterion suggested by Rotterdam ESHRE/ASRM group (2003), but stated that subphenotypes should be considered.

The prevalence of PCOS is 8-13%.[1] Ethnic differences are also reported in the clinical manifestation of the syndrome. The Modified Ferriman-Gallwey scales (mFG) and cut-off values for hormones levels need to be individualized to a particular ethnicity.[1]

It is seen that this syndrome has a familial distribution thus suggesting a genetic cause in its etiopathogenesis. However, the etiology may lie in both genetic and environmental factors with stress and lifestyle also playing a role.[2] The first time it was noticed in 1968 by Cooper *et al.* that this disease runs in families. The inheritance was initially thought to be autosomal dominant. Over the course of time it was found to be polygenic.[3] The genetic nature of the disease was further established when twins were studied. Data from twins was analyzed by Vink *et al.*[4] who found the occurrence in monozygotic twin sisters (tetrachoric correlation 0.71) for PCOS was about twice as large as in dizygotic twin and other sisters (tetrachoric correlation 0.38).[5]

Since, PCOS acts by various pathways which make it a multifactorial disorder, not one but various genes may be involved. Through these genes there may be an endocrinal manifestation impacting fertility. Although, a genetic etiology is established, exact consensus has not been achieved as to the number of genes involved and how they act. The protein pathways could be impacted leading to endocrine manifestations and clinical symptoms. The complex heterogeneity also exists within families thus showing up as varied clinical features and severity within one family. This has lead to a difficulty in isolating a single gene as accountable. Over the years studies have shown an involvement of multiple genes to varying degrees.[6]

It is important to identify the genes with their variants and establish their interaction. This interaction may be responsible for creating an endocrine and physical influence which leads to manifestation of PCOS symptoms. This would enable us to understand the pathophysiology of PCOS and help treat infertility and other manifestation in a structured way.

Candidate gene polymorphism studies are a methodology which was applied to study various genetic aspects of PCOS in relation to endocrine and metabolic manifestations. To overcome pitfalls in this method relating to proving association and its strength Genome-wide method has been introduced.

Genes associated with PCOS

Genes associated with PCOS which have been identified are classified as[7]

(1) Genes involved in steroidogenesis: CYP 11, CYP 17, CYP 21
(2) Genes involved in steroid hormone effects: Androgen receptor gene, sex hormone-binding globulin gene
(3) Genes involved in gonadotrophin release regulation and action: LH gene, LH receptor gene, FSH Receptor gene.
(4) Genes involved in insulin secretion and action: Variable number tandem repeats (VNTR), Insulin receptor gene, Insulin receptor substrate proteins (IRS-1 and IRS-2), Calpain 10
(5) Genes involved in adipose tissue metabolism: Leptin gene, Leptin receptor gene, Peroxime proliferator-activated receptor-γ, FTO gene

Steroidogenesis is affected through genes in ovaries and adrenals. Hormonal impacts are seen because androgen, estrogen, FSH and LH receptors genes could be involved.

The sex hormone binding globulin gene could also be affected. Metabolic manifestation may occur through the effect on the genes affecting insulin and adipose tissue metabolism.

Hyperandrogenemia often has a hereditary basis. Hence, genes affecting adrenals and ovary may be responsible for this clinical manifestation. One of the genes implicated was CYP11a as this gene impacts the step of P450 cholesterol side chain cleavage.[8] Prevalence of CYP21 mutations has also been seen in PCOS. 21-OH is a cytochrome P450 which mediates conversion of 17-hydroxyprogesterone to 11-deoxycortisol. Deficiency causes decreased cortisol production leading to high levels of ACTH due to loss of negative feedback by cortisol. The increased levels of ACTH cause a higher androgen production leading to clinical manifestations like acne and hirsutism.[9] Other genes which may have an effect on manifestation of hyperandrogenemia are CYP 17 and CYP 19. CYP19 is responsible for high levels of androgens as it acts on the aromatase activity. Aromatase converts androgens into estrogens and any malfunction of this enzyme would lead to higher androgens in these women.[10]

Structural alterations and mutations in androgen receptor (AR) gene which is located on the X chromosome may lead to manifestation of hyperandrogenemia in PCOS.[11] In a study by Hickey *et al*.[12] infertile women with PCOS exhibited a greater frequency of CAG alleles or biallelic in AR gene compared with both the fertile control group ($P < 0.05$) and the general population ($P < 0.01$). AR (CAG) gene locus and/or its differential methylation patterns influence the disease process leading to PCOS manifestations. A meta analysis conducted in 2013 showed no association with CAG length variation in androgen receptor with PCOS. However, the length seemed to be directly proportional to testosterone levels in these women thus showing an indirect effect.[13]

Another gene which is involved is the sex hormone binding globulin gene. Sex Hormone binding globulin (SHBG) binds the androgens and other hormones thus influencing the levels of free androgens in the body. SHBG gene is in chromosome 17p13-p12. Alteration in this gene can lead to the hyperandrogenemia. Insulin and metabolic factors are also known to influence levels of SHBG.[14]

AMH gene is a gene involved in gonadotropic secretion. There were many variants of AMH gene identified in women who had PCOS. Decreased AMH signaling may lead to increased androgens because of removal of inhibitory influence of CYP 17 activity.[15]

The LH receptor gene may be affected leading to endocrinal imbalances. Point mutation and polymorphism in the beta subunit of LH has been seen. This may lead to raised LH levels as seen in PCOS.[16] FSH polymorphism is also associated with PCOS.[17] Multiple variants at FSHR showed prominent variant located in the intron of FSHR. The A allele of rs2300441 led to a low value of FSH in the PCOS group.[18] Association of estrogen receptor gene variants (ESR1 and ESR2) was seen with polycystic ovary syndrome It was also found that LH, LH/FSH or hyperandrogenism were correlated and even more significant correlation with metabolic syndrome (rs9340799) and hyperglycemia (rs3798577).[19]

There is an association between PCOS and obesity, the direction and mechanism underlying this relationship are not known. It was earlier thought that PCOS causes an increased BMI. However, in a study by Brower *et al*.[20] each standard deviation of genetically higher BMI was associated with a 4.89 higher odds of PCOS. Infact, vice versa was not true ie genetic risk of PCOS did not influence BMI. A Bidirectional Mendelian randomization analyses was done concluding that high BMI is causal for PCOS while the reverse is not the true. As BMI impacts the development of PCOS it is important that patients are counseled and weight loss and life style changes are tried for their ability to prevent or treat PCOS before complications like infertility and metabolic syndrome set in.

Adipose metabolism genes like Leptin gene, Leptin receptor gene, Peroxime proliferator-activated receptor-γ and FTO have been associated with PCOS [1] Fat mass and obesity-associated protein (FTO) is an enzyme on chromosome 16. A recent meta-analysis found a relationship between FTO gene polymorphism and weight which was twice that in general population with polymorphism. It was discovered that the impact of the FTO variant on BMI is greater in women with PCOS compared to normal controls. This signifies that PCOS itself may amend the action of *FTO* on BMI through the metabolic changes seen in these women. Hence, PCOS modifies the influence of FTO on weight and BMI.[21] The variant rs9939609 is associated with high levels of testosterone and metabolic symptoms in PCOS.[22]

Insulin action gene, variable number tandem repeats (VNTR) regulates insulin gene expression and may

help in causing type II Diabetes mellitis in PCOS patients Many studies have found an association in the genes of insulin receptor, insulin receptor substrate IRS-1 and IRS-2, and proliferator-activated receptor gamma (PPAR-γ) with PCOS[23] Calpain 10 gene also interferes with the insulin metabolism.

A very recent genome-wide association study of polycystic ovary syndrome identified from electronic health records gave further insights into the genetic of PCOS.[24]

Epigenetic changes

Genetic studies have been limited in recognizing genetic loci despite the fact that PCOS shows an inherited trend. Common variants in genes are unable to answer this familial trend in PCOS. It is possible that it is not a genomic variation but an epigenetic trend which may be causing an effect. In epigenetic changes there is no change in DNA sequence. Methylation of DNA causes an altered gene expression which leads to various phenotypes. These are heritable and hence phenotypes show an ethnicity. Epigenetic change may also occur due to environmental factors making in utero environment crucial to development of PCOS.

Genome-wide DNA methylation studies show that altered methylation of genes causing inflammation, hormone synthesis and signaling and glucose and lipid metabolism are seen in PCOS, thus causing clinical manifestations of PCOS like hyperandrogenism and insulin resistance. These changes have been found in ovary, adipose tissue and skeletal tissue. More research is warranted in this field.[25]

CONCLUSION

PCOS, a polygenic and multifactorial disorder, which goes beyond reproductive pathologies yet, its etiology still remains in many ways unknown despite much research in the field. There are genetic variants responsible for insulin resistance and reproductive manifestations. Genetic studies have traced the metabolic and endocrine pathways of this disease in an attempt to establish a link. Genome Wide Association Studies (GWAS) is an ideal method to identify this link in a heterogenous disorder like PCOS. Research is ongoing on relevant variants in genes which increase incidence and susceptibility to PCOS and influence the severity of manifestation of symptoms. Epigenetic changes are also being studied. The problem faced is lack of uniform diagnostic criterion ethnic variations and impact of environment. The future is to identify these genes as biomarkers for PCOS.

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Conflicts of interest

There are no conflicts of interest.

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