Present status of understanding on the genetic etiology of polycystic ovary syndrome

Dasgupta S, Mohan Reddy B

ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age characterized by chronic anovulation or infrequent ovulation, obesity, hirsutism, hyperandrogenism and numerous follicular cysts in enlarged ovaries. PCOS is the leading cause of anovulatory infertility among premenopausal women. Such patients are also at increased risk for obesity, insulin resistance (IR), type-2 diabetes mellitus, premature arteriosclerosis and endometrial cancer. Consequently, PCOS has significant implications for the health and quality of life of these patients. PCOS was firstly reported as Stein-Leventhal syndrome in 1935, and since then has attracted more and more attention due to its genetic heterogeneity and diverse clinical manifestations. It has been used as an important clinical model to investigate the relationships among endocrine functions, reproductive activity and energy metabolism.[1]

There is no consensus on the diagnostic criteria and definitions of PCOS. Until recently, two definitions were followed: one is the National Institute of Child Health and Human Development (NICHD) conference diagnostic criteria[2] and the other is suggested by the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM).[3] The third definition has been proposed recently by the Androgen Excess Society, which takes into account both the criteria existent till date. The three definitions are summarized in Table 1. Diagnosing a woman as having PCOS implies serious health consequences and thus a judicious definition of PCOS is necessary to guide current and future research work. It is also now recognized that the definition of this syndrome will continue to evolve over time, incorporating new research findings.[4] The Venn diagram (Figure 1) depicts the variability in clinical phenotypes characterizing PCOS cases.

A number of studies have been performed to assess the prevalence of polycystic ovaries on ultrasound examination in the general female population of fertile age. A limited number of studies conducted so far (Table 2) suggest that it is an extremely prevalent syndrome, which varies from about 5% in USA[7] to as high as 33% in UK.[8] Apart from the study conducted on Thai women,[9] all the others were largely on Caucasian populations; the prevalence rate of PCOS for black and white women in USA is not significantly different.[10]

Pathophysiology of PCOS and the Major Health Implications

The pathological conditions result from the endocrine, metabolic and cardiovascular mechanisms. However, how much each
with the process of follicular maturation. Compared with the follicular phase of the normal menstrual cycle, women with PCOS exhibit a disproportionately high luteinizing hormone (LH) secretion with relatively constant low follicle stimulating hormone (FSH) secretion [Figure 3]. The pattern of steroid secretion in polycystic ovary suggests a generalized dysregulation of ovarian androgen secretion, which is further augmented by insulin. PCOS is, thus, characterized by a metabolic disorder in which hyperinsulinaemia and peripheral IR are central features. The characteristic disturbances of insulin secretion and action are much more prominent in PCOS women with amenorrhoea or anovulatory menses than in equally hyperandrogenic women with regular cycles.[20,21]

Insulin and FSH have a synergistic effect on estrogen production in granulosa cells from anovulatory PCO, which is not seen in the majority of ovulatory patients. Insulin also seems to produce a greater increase in androgen production by theca cells isolated from PCOS women than controls.[22,23] Another mechanism contributes to developing PCOS is still unknown. The schematic representation of these mechanisms involved in the heterogeneous manifestation of the PCOS is presented in Figure 2. The endocrine component specifically deals with the abnormal steroid synthesis from ovaries and adrenals resulting in high androgen levels. An inappropriate gonadotropin secretion is associated with the PCOS women exhibiting classic form of PCOS, i.e. hyperandrogenaemia, polycystic ovaries, chronic anovulation, hirsutism and obesity. On the contrary, the non-classical form is a more subtle condition usually found among lean women who manifest some of the above features associated with PCOS. Although androgens are obligate substrates for estrogen synthesis, an excess of androgens seem to interfere

### Table 1: Diagnostic criteria for polycystic ovary syndrome according to different published definitions

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis criteria</strong></td>
<td>Requires simultaneous presence of:</td>
<td>Requires the presence of at least two criteria:</td>
</tr>
<tr>
<td>1. Clinical and/or biochemical hyperandrogenism</td>
<td>1. Clinical and/or biochemical hyperandrogenism</td>
<td>1. Oligo-anovulation or</td>
</tr>
<tr>
<td>2. Menstrual dysfunction</td>
<td>2. Ovulatory dysfunction</td>
<td>2. PCOM</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Congenital adrenal hyperplasia, androgen secreting tumours, Cushing’s syndrome and hyperprolactinaemia</td>
<td>Congenital adrenal hyperplasia, androgen secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing’s syndrome, syndromes of severe insulin resistance, thyroid dysfunction and hyperprolactinaemia</td>
</tr>
<tr>
<td><strong>Clinical traits</strong></td>
<td>Hirsutism, alopecia and acne</td>
<td>Hirsutism, acne and androgenic alopecia</td>
</tr>
<tr>
<td><strong>Biochemical traits</strong></td>
<td>1. Total testosterone</td>
<td>1. Free androgen index or free testosterone</td>
</tr>
<tr>
<td>2. Free testosterone</td>
<td>2. Total testosterone</td>
<td>2. Total testosterone</td>
</tr>
<tr>
<td>3. Androstenedione</td>
<td>3. DHEA</td>
<td>3. DHEA</td>
</tr>
<tr>
<td><strong>PCOM</strong></td>
<td>Not included</td>
<td>At least one ovary showing either:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Twelve or more follicles or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2-9 mm in diameter) or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Ovarian volume - 10 ml</td>
</tr>
</tbody>
</table>

NICHD - National Institute for Child Development and Human Diseases, AES - Androgen Excess Society, PCOM - polycystic ovary morphology, DHEA - dehydroepiandrosterone, adapted from codner and escobar-morreale, 2007[3]

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Figure 1: A Venn diagram of reproductive phenotypes in PCOS whose definition is variable depending on the union or intersection of phenotypes (PCO - polycystic ovaries, HPCO - hyperandrogenism and polycystic ovaries, HCA - hyperandrogenism and chronic anovulation, PCO-CA - polycystic ovaries and chronic anovulation, HCA-PCO - hyperandrogenism, chronic anovulation and polycystic ovaries)[6]

Table 2: Prevalence of PCOS in different geographical regions

<table>
<thead>
<tr>
<th>Place of study</th>
<th>Prevalence (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama, USA</td>
<td>4.7</td>
<td>Knochenhauer et al., 1998[7]</td>
</tr>
<tr>
<td>Alabama</td>
<td>8</td>
<td>Aziz et al., 2004[11]</td>
</tr>
<tr>
<td>Thailand</td>
<td>5.7</td>
<td>Vutyanovitch et al., 2007[9]</td>
</tr>
<tr>
<td>Spain</td>
<td>6.5</td>
<td>Asunción et al., 2000[12]</td>
</tr>
<tr>
<td>Lesbos (Greek Island)</td>
<td>9</td>
<td>Diamanti-Kandarakis et al., 1999[13]</td>
</tr>
<tr>
<td>Greece</td>
<td>17</td>
<td>Botis et al., 1995[14]</td>
</tr>
<tr>
<td>New Zealand</td>
<td>21</td>
<td>Farquhar et al., 1994[15]</td>
</tr>
<tr>
<td>Sheffield, UK</td>
<td>21</td>
<td>Cresswell et al., 1997[16]</td>
</tr>
<tr>
<td>Middlesex, UK</td>
<td>22</td>
<td>Clayton et al., 1992[17]</td>
</tr>
<tr>
<td>London, UK</td>
<td>25</td>
<td>Polton et al., 1988[18]</td>
</tr>
<tr>
<td>Oxford, UK</td>
<td>33</td>
<td>Michelmore et al., 1999[8]</td>
</tr>
</tbody>
</table>

with the process of follicular maturation. Compared with the follicular phase of the normal menstrual cycle, women with PCOS exhibit a disproportionately high luteinizing hormone (LH) secretion with relatively constant low follicle stimulating hormone (FSH) secretion. The pattern of steroid secretion in polycystic ovary suggests a generalized dysregulation of ovarian androgen secretion, which is further augmented by insulin. PCOS is, thus, characterized by a metabolic disorder in which hyperinsulinaemia and peripheral IR are central features. The characteristic disturbances of insulin secretion and action are much more prominent in PCOS women with amenorrhoea or anovulatory menses than in equally hyperandrogenic women with regular cycles.[20,21]

Insulin and FSH have a synergistic effect on estrogen production in granulosa cells from anovulatory PCO, which is not seen in the majority of ovulatory patients. Insulin also seems to produce a greater increase in androgen production by theca cells isolated from PCOS women than controls.[22,23] Another
common clinical feature of PCOS is obesity. Approximately 50% of PCOS women are overweight or obese. The history of the weight gain frequently precedes the onset of oligomenorrhea and hyperandrogenism, suggesting a pathogenetic role of obesity in the subsequent development of the syndrome.\(^{24}\) Endothelial dysfunction has been observed in PCOS women. Chronic inflammatory markers, such as TNF-\(\alpha\) and Interleukin-6 (IL-6), promote IR and hyperandrogenism and therefore have been implicated in PCOS pathophysiology.\(^{25}\) Women with PCOS also exhibit lower high-density lipoprotein (HDL) levels, higher triglyceride and higher low-density lipoprotein (LDL) levels than age- and weight-matched control women, which is responsible for the increased incidence of hypertension, coronary heart disease and thrombosis.\(^{26}\) There is also an increased prevalence of endometrial hyperplasia and carcinoma in women with the PCOS.\(^{27,28}\)

Further studies are required to determine the incidence of such pathological conditions in PCOS women. Such women usually seek pre-emptive screening in their initial reproductive years, which is too early for the accumulative effects of some of these risk factors to culminate into the disease. Large multi-site simultaneous collaborative studies are necessary to evaluate the actual incidence and long-term health consequences of this syndrome.\(^{29}\)

Etiology: Role of Genetic and Environmental Factors

Genetic background

Familial clustering of PCOS has been consistently reported suggesting that genetic factors play a role in the development of this syndrome, although PCOS cases do not exhibit a clear pattern of Mendelian inheritance. It is now well established that PCOS represents a complex trait similar to type-2 diabetes and obesity, and that both genetic and environmental factors contribute to the PCOS pathogenesis. Overall, PCOS can be viewed as a heterogeneous androgen excess disorder with varying degrees of gonadotropic and metabolic abnormalities.\(^{22}\) However, there is strong evidence for a major genetic component in the etiology of PCOS. In families with PCOS cases, there is evidence for heritability of both hyperandrogenaemia and hyperinsulinaemia in affected siblings.\(^{30-32}\) Numerous genetic mechanisms, including autosomal dominant, modified autosomal dominant, X-linked dominant and multifactorial, have been proposed, still, the precise mode of inheritance of PCOS has not been established.\(^{33}\) It has been suggested that multiple loci and epigenetic modifications may play a role in the phenotype.\(^{34}\) Family history, as a reflection of genetic risk, can also be considered as a risk factor and, therefore it is important for determining an individual’s risk of developing PCOS.\(^{35}\)
Genetic models of PCOS

While most studies have focused on defining the characteristics of this disorder, a few have attempted to elucidate the genetic mechanisms behind the development of PCOS. The approach depends, to a significant degree, on whether the disorder is viewed as the combination of defects unique to this syndrome or as defects already present in the general population.\[35\] With this in mind, three general genetic models of PCOS have been proposed:

1. The first one, termed as the “single-gene Mendelian” model, considers that the majority of the defects present in PCOS are unique. This model would suggest that the inheritance of PCOS should demonstrate a recessive or dominant pattern, indicative of a single-gene defect. If a dominant mode of transmission is assumed, all women who inherit the defect would develop clinically evident PCOS.

2. The second model, termed “multifactorial”, suggests that the defects present in PCOS are not unique to it, and this disorder simply represents the conglomeration of abnormalities already present in the general population. Under this concept, PCOS would be considered as a multifactorial genetic disorder such as NIDDM and CVD. Hence, women carrying multiple defects (both via inheritance and via environmental influences) would be at increasing risk of developing clinical PCOS.

3. The third model, or the “variable expression-single gene” model, is a modified combined version of the above two models. Under this model, PCOS is caused by a major gene defect, which is transmitted to 50% of offspring. However, the expression of PCOS would then be modified by additional factors, both environmental and/or genetic (i.e. “genetic background”), so that the actual observed segregation ratio could be less than expected for an autosomal dominant disorder (0.5). Theoretically, women who possess the mutation would be at almost 100% risk of developing some degree of PCOS, although additional factors would determine the clinical severity of the disorder. Genetically predisposed women not exposed to these other influences might develop only subclinical forms of PCOS, or present with isolated diagnostic features seen in PCOS (e.g. hyperandrogenaemia only), but not the full disorder.

Methods used to study genetics of PCOS using candidate genes

The candidate gene approach relies upon improved molecular genetic techniques and statistical methods to analyze potential genes based on biological plausibility. Pathways that affect steroidogenesis, IR, gonadotropin function and obesity provide potential genes for investigation.\[34\] The finding of abnormalities in the earliest gonadotropin-independent stages of ovarian follicle development suggests that genes involved in folliculogenesis must also be considered as candidates for the etiology of PCOS.
To understand genetic etiology of PCOS, two mainstream approaches are employed: (i) association studies and (ii) linkage studies. Within these two approaches, three different study designs are adopted: (i) case-control study, (ii) affected sib-pair study (ASP) and (iii) transmission-disequilibrium test (TDT). Out of these three study designs, the case-control study design is mostly followed for the genetic analysis of PCOS. Genome-wide association studies are now feasible and can provide an additional means for identifying genes related to complex disorders. This approach combines the best features of linkage with the strength of association approaches. The whole genome scan approach utilizing the single nucleotide polymorphism (SNP) microarray gene chip technology brings the highest resolution in genetic mapping. Yet, there is no PCOS study published with this technique. In addition to this, the HapMap project brings further power to the association studies by genotyping over a million SNPs and characterizing patterns of genetic variation in linkage disequilibrium.[2]

The candidate genes implicated in the etiology of PCOS along with their chromosomal location and functions are presented in Table 3. A comprehensive review has been done by Unluturk et al.,[2] for all the candidate gene association studies in PCOS. For most of the genes, there have been more negative results (i.e. no association with PCOS) than positive except for few genes as illustrated in Figure 4. However, the inconsistent nature of data need not necessarily rule out the role of these candidate genes showing relatively lesser number of positive associations given that, overall, the major difference between the studies with and without significant association lies in the study design and the sample size. Most of the studies that have yielded positive results are case-control studies aiming at identifying SNP variation in various candidate genomic regions [Table 4] and are based on large sample sizes. Therefore, future studies with candidate gene approach focusing on larger samples from genetically homogenous populations would be fruitful.

**PCOS and epigenetics**

Few studies have attempted to understand the etiology of PCOS through an epigenetic perspective by considering the

![Figure 4: Bar diagram depicting number of studies with and without association between PCOS and different candidate genes](image)

### Table 3: Candidate genes in polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr. location</th>
<th>Codes for</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes involved in ovarian and adrenal steroidogenesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP11a</td>
<td>15q23-24</td>
<td>P450 cytochrome scc enzyme</td>
<td>Conversion of cholesterol into progesterone</td>
</tr>
<tr>
<td>CYP21</td>
<td>6p21.3</td>
<td>21-hydroxylase enzyme</td>
<td>Conversion of 17-OHP into 11-deoxycortisol</td>
</tr>
<tr>
<td>CYP17</td>
<td>10q24.3</td>
<td>P450C17α enzyme</td>
<td>Conversion of pregnenolone and progesterone into DHEA and androstenedione</td>
</tr>
<tr>
<td>CYP19</td>
<td>15q21</td>
<td>P450arom</td>
<td>Conversion of androgens to estrogens</td>
</tr>
<tr>
<td>Genes involved in steroid hormone effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen receptor gene (AR)</td>
<td>Xq11.2</td>
<td>Androgen receptor</td>
<td>Nuclear transcription factor</td>
</tr>
<tr>
<td>Sex hormone binding globulin gene (SHBG)</td>
<td>17p13.2</td>
<td>Sex hormone binding globulin</td>
<td>Regulates access of androgens to target tissues</td>
</tr>
<tr>
<td>Genes involved in gonadotropin action and regulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteinizing hormone (LH) gene</td>
<td>19q13.32</td>
<td>β-subunit of LH</td>
<td>Responsible for LH specificity</td>
</tr>
<tr>
<td>Follistatin gene (FST)</td>
<td>5q11.2</td>
<td>Follistatin</td>
<td>High affinity binding protein for activin</td>
</tr>
<tr>
<td>Genes involved in insulin action and secretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin gene (INS)</td>
<td>11p15.5</td>
<td>-</td>
<td>Insulin action and secretion</td>
</tr>
<tr>
<td>Insulin receptor gene (INSR)</td>
<td>19p13.3</td>
<td>Insulin receptor</td>
<td>Insulin action and secretion</td>
</tr>
<tr>
<td>Insulin receptor substrate genes (IRSs)</td>
<td>2q36</td>
<td>Insulin receptor substrates</td>
<td>Promote metabolic activities of insulin</td>
</tr>
<tr>
<td>Calpain-10 gene (CAPN10)</td>
<td>2q37.3</td>
<td>Calpain 10 (cysteine protease)</td>
<td>Insulin secretion and action</td>
</tr>
<tr>
<td>Genes involved in energy homeostasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The genes of leptin</td>
<td>7q31.3-32.1</td>
<td>Leptin (adipocytokine)</td>
<td>Energy metabolism</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>3q27</td>
<td>Adiponectin</td>
<td>E energy metabolism</td>
</tr>
<tr>
<td>PPAR-γ gene</td>
<td>3p25</td>
<td>PPAR-γ</td>
<td>Transcription factor involved in adipogenesis, energy metabolism and a functional receptor</td>
</tr>
</tbody>
</table>

for thiazolidinediones (TZDs), Genes involved in chronic inflammation

| TNF-α                      | 6p21.3        | TNF-α                            | Adipocyte cytokine                                                        |
| TNFR2 gene                 | 1p36.2        | TNFR2 Receptor                    | Mediator of TNF-α actions                                                 |
| IL-6                       | 7q21          | IL-6                             | Stimulation of the hypothalamic pituitary-adrenal axis and modulation of lipid metabolism |

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X-chromosome inactivation (XCI) patterns in PCOS cases. These studies have taken into account the trinucleotide (CAG) repeat of the androgen receptor (AR) gene. Initially, Mifsud et al.\[41\] investigated the role of these CAG repeats in PCOS by undertaking a case-control study. A longer repeat stretch was observed in patients with high serum androgen levels than the patients with a lower serum androgen level. Another study compared the frequency distributions of CAG repeat alleles and their pattern of expression via X-inactivation analysis among 83 fertile women and 122 infertile women with PCOS.\[42\] The findings warrant a closer inspection of XCI between sister pairs with the same genotype at the polymorphic locus on the X-chromosome.\[73\] The main feature of the outcome of this study was mRNA abundance of oocyte-expressed genes. Cluster analysis revealed differences in global gene expression profiles between normal and PCOS oocytes. Three hundred and seventy-four genes showed significant differences in mRNA abundance in PCOS oocytes, of which some were associated with chromosome alignment and segregation during mitosis and/or meiosis, whereas others contained putative AR and/or peroxisome proliferating receptor binding sites.

**Male equivalent of PCOS**

Complexity of the symptoms in close relatives of women with PCOS along with its probable autosomal inheritance pattern initiated a hypothesis about the existence of a male equivalent of PCOS. Although the male phenotype of PCOS is still not established and is one of the challenges for the genetic studies of PCOS, Dusková et al.\[75\] suggested premature alopecia as one of the signs of a male phenotype of this syndrome. Their study investigated a group of 30 men, in which premature hair loss started before 30 years of age. Approximately one-third of the prematurely balding men expressed subnormal levels of serum hormone binding globulin (SHBG) and an imbalance between LH and FSH, like women with PCOS. Another finding of this study was a significantly higher frequency of decreased insulin sensitivity. Thus, a final proof of existence of the male equivalent of PCOS might be important not only for closer studies of pathogenesis and genetic background of PCOS, but also for general medical application. The occurrence of androgenic alopecia, especially before the age of 30 years, may

**Table 4: Polycystic ovary syndrome candidate gene association studies**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variation*</th>
<th>Genomic region</th>
<th>Study design</th>
<th>Reference Nos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP11a</td>
<td>VNTR</td>
<td>Promoter region</td>
<td>FL, CC</td>
<td>2, 36</td>
</tr>
<tr>
<td>CYP21</td>
<td>SNPs</td>
<td>Exon 1, 7, 8, 10, Intron 2</td>
<td>CC</td>
<td>2, 37</td>
</tr>
<tr>
<td>CYP 17</td>
<td>SNPs</td>
<td>Promoter region</td>
<td>FL, CC</td>
<td>2, 13, 38, 39</td>
</tr>
<tr>
<td>CYP 19</td>
<td>VTR/SNP</td>
<td>Promoter region</td>
<td>FL, CC</td>
<td>2</td>
</tr>
<tr>
<td>AR</td>
<td>CAG repeat</td>
<td>Exon 1</td>
<td>CC</td>
<td>2, 40-44</td>
</tr>
<tr>
<td>SHBG</td>
<td>VNTR</td>
<td>Promoter region</td>
<td>FL, CC</td>
<td>40</td>
</tr>
<tr>
<td>LH</td>
<td>SNP</td>
<td>Exon 8</td>
<td>CC</td>
<td>2</td>
</tr>
<tr>
<td>Follicatin</td>
<td>SNPs</td>
<td>Promoter region</td>
<td>FL, CC</td>
<td>40, 48-50</td>
</tr>
<tr>
<td>INS</td>
<td>VNTR</td>
<td>5′ regulatory region</td>
<td>FL, CC</td>
<td>40, 51-55</td>
</tr>
<tr>
<td>INSR</td>
<td>SNPs</td>
<td>Exons</td>
<td>FL, CC</td>
<td>40, 56-58</td>
</tr>
<tr>
<td>IRSs</td>
<td>SNPs</td>
<td>-</td>
<td>CC</td>
<td>59-61</td>
</tr>
<tr>
<td>Calpain</td>
<td>SNPs</td>
<td>Exon 10, intron 3, 6, 13</td>
<td>CC</td>
<td>62-66</td>
</tr>
<tr>
<td>Leptin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>SNPs</td>
<td>Exons/Introns</td>
<td>CC</td>
<td>67, 68</td>
</tr>
<tr>
<td>PPAR-γ gene</td>
<td>SNPs</td>
<td>Exon 2, 6</td>
<td>FL, CC</td>
<td>2, 40</td>
</tr>
<tr>
<td>TNF-α gene</td>
<td>SNPs</td>
<td>Promoter region</td>
<td>CC</td>
<td>2, 69</td>
</tr>
<tr>
<td>TNFR2 gene</td>
<td>SNP</td>
<td>Exons</td>
<td>CC</td>
<td>2, 70</td>
</tr>
<tr>
<td>IL-6</td>
<td>SNP</td>
<td>Regulatory region</td>
<td>CC</td>
<td>2, 71</td>
</tr>
<tr>
<td></td>
<td>SNP/STRs</td>
<td>Receptor genes</td>
<td>CC</td>
<td>2, 72</td>
</tr>
</tbody>
</table>

*Variation: VNTR - variable number tandem repeats, SNPs - single nucleotide polymorphisms, STRs - short tandem repeats, FL - family linkage studies, CC - case-control studies

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be considered as a mark of potentially increased risks of serious diseases in the later age.

**Challenges for genetic studies**

Obstacles, such as phenotypic variability, lack of a male phenotype, multiple attempts at analysis and small sample sizes that hamper the efforts towards understanding the genetic basis of PCOS, are outlined in Table 5. Nevertheless, great care must be taken to apply rigorous standards as we proceed with genetic studies.  

Environmental Factors

While clustering of cases in families strongly support the role of genetic factors in the development of PCOS, heterogeneity of phenotypic features in different families and even within the same family underscores the importance of the environmental contribution. The highly variable phenotype of PCOS suggests that apart from genes other factors may contribute to the development of the disorder. These factors might include environmental influences such as fat and carbohydrate consumption, exercise level, peripubertal stress and/or hormonal exposure.

Prenatal: Hormonal exposure in the uterine environment

The etiology of PCOS remains unclear and the heterogeneity of clinical and biochemical features has raised the question about whether PCOS represents the common end point of several aetiological factors. Abbott et al. have proposed a hypothesis, which states that PCOS is a genetically determined ovarian disorder characterized by excessive androgen production and that the heterogeneity can be explained on the basis of the interaction of this disorder with other genes and with the environment. This hypothesis is based on data from animal models and is supported by clinical studies. It is suggested that, in human females, exposure to excess androgen, at any stage from foetal development of the ovary to the onset of puberty, leads to many of the characteristic features of PCOS including abnormalities of LH secretion and IR. To sum up, exposure of the foetal hypothalamic-pituitary-ovarian axis to excess androgens influences the dynamics of early follicular development and can set up a train of events, which result in both the reproductive and metabolic consequences of PCOS.

Postnatal: Diet, nutrition and obesity

In postnatal life, the natural history of PCOS can be further modified by factors affecting the insulin secretion and/or action, most importantly, nutrition. Diet is a well-known factor playing a role in the regulation of sex steroid metabolism. Several studies have demonstrated that high-lipid and low-fibre diet is related to an increase in androgen circulating levels. In some reports, PCOS women were found to have a higher intake of saturated lipids and a lower intake of fibres when compared to control groups. Low-fibre and high-lipid intake has been considered as one of the nutritional factors, which favour the onset and development of obesity in industrialized countries. Therefore, it can be speculated that a low-fibre and high-lipid diet may act negatively on sex steroid metabolism in selected groups of PCOS women, by increasing androgen availability and by favouring the development of obesity. Obesity is a major feature in women with PCOS, and evidence suggests that obesity contributes to the pathogenesis of PCOS by aggravating the intrinsic IR of these women.

**Theories behind etiology of PCOS**

Odunsi and Kidd have put together the main theories that have been proposed in previous studies regarding etiology of PCOS.

1. The luteinizing hormone-theca interstitial cell (LH-TIC) theory suggests that the pathophysiologic mechanisms leading to abnormally elevated levels of LH underlie the phenomenon of PCOS. The theory suggests that high levels of circulating LH cause an increase in the growth of TIC in developing follicles, which leads to androgen overproduction and follicular atresia.

2. The follicle stimulating hormone-granulosa cell (FSH-GC) theory suggests that the reduced FSH leads to subnormal induction of cytochrome P450 aromatase in the granulosa cells, leading to elevated androgen levels.

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**Table 5: Limitations in the genetic susceptibility studies of polycystic ovary syndrome**

| Lack of universally accepted diagnostic criteria and definition | • NICHD criteria  
| | • Ultrasonographic criteria  
| | • Rotterdam criteria  
| | • Premature baldness  
| | • Increased pilosity  
| | • Increased DHES levels  
| | • Exaggerated responses to GnRH and ACTH  
| | • Insulin resistance, glucose tolerance  
| Heterogeneity of male phenotype | • Potential statistical error  
| | • Difficulty in studying more than one generation  
| | • Ascertainment bias  
| | • Autosomal dominant  
| | • Monogenic  
| | • X-linked  
| Relatively small sample size of the study populations | • Difficulty in assignment of the phenotype (affected versus unaffected)  
| | • Involvement of multiple genes  
| | • Compensatory adaptation; through hormonal treatment, nutritional control  
| Affected reproduction | •  
| Non-random ascertainment of families | •  
| Obscurity in the mode of inheritance | •  
| Variable penetrance and expressivity | •  
| Locus heterogeneity | •  
| Environmental interactions | •  

Adapted from Unluturk et al. 2007 [2]
This may be due to insufficient bioactive FSH in the follicular microenvironment to induce P450 aromatase gene expression, dysfunctional FSH receptor signal transduction mechanism, or the presence of inhibitors (such as epidermal growth factor and insulin-like growth factor (IGF)-binding protein 3) that prevent the normal expression of P450 aromatase activity.

3. The third theory relates to the growth factor - autocrine-paracrine system. In PCOS, there is evidence of an altered IGF/insulin system, and these act as mediators of biologic responses of the selectogenic and atretogenic follicular hormones.

Evolutionary Perspectives and Impact of Ethnicity

Polycystic ovary syndrome is neither population-specific nor restricted to any particular geographical region, its worldwide frequency is very high, affecting 5-10% of women of reproductive age. Eggers et al. attempted to provide an evolutionary explanation for the high frequency of PCOS. According to this hypothesis, PCOS women may have reproductive advantage via kin selection because it seems plausible that childless women try to help to bring up the offspring of near relatives. This behaviour may increase their inclusive fitness and thus the high prevalence rates of PCOS may be the result of evolutionary mechanisms such as kin selection. However, other evolutionary processes associated with PCOS still have to be scrutinized.

Studies highlighting the impact of ethnicity on the presentation of PCOS basically have taken into consideration the metabolic aspects of the syndrome, which include IR, glucose intolerance, lipid abnormalities and coronary artery diseases. Williamson et al. conducted a cross-sectional study of women of European, Māori, Pacific Island, Indian and Chinese origin for clinically and ultrasonically diagnosed PCOS. According to this study, European and Māori women were more likely to present with hirsutism than other ethnic groups, whereas Māori and Pacific Island women were more obese and had the highest rates of IR and lipid abnormalities. Other comparative investigations have revealed that Indian PCOS subjects had higher insulin responses compared to the cases with white ethnic background. The ethnic difference was less pronounced in obese women. In addition, PCOS is reported to be more prevalent in South Asian women residing in the UK than the native Caucasians.

Hyperhomocysteinaemia is a recognized risk factor for atherosclerosis, particularly among migrant South Asians, and has recently been shown to be correlated positively with the degree of IR/hyperinsulinaemia. Subsequently, another study by Wijeyaratne et al. showed that elevation of fasting plasma homocysteine in PCOS varies with ethnicity and correlates significantly with fasting insulin. High homocysteine in young Sri Lankans with PCOS has major implications for their long-term risk for atherosclerosis. The incidence of IR is higher in Mexican American women with PCOS than in native white women. While Japanese PCOS subjects might have insulin resistance but the factor of obesity has a stronger effect on insulin resistance than the existence of PCOS. A general outcome of the above-mentioned studies demonstrates that the ethnic background of subjects with PCOS needs to be considered in studies on the metabolic parameters. In particular, the normative values for IR screening in the PCOS population should be individualized for different racial or ethnic populations.

Indian Scenario

Population structure

Population substructure and recent admixture may confound the results of genetic association studies in unrelated individuals, leading to a potential excess of both false positive and false negative results. The possibility of false associations depends on the sampled population, the trait being studied and the marker being tested. Ongoing modernization in India has elevated the prevalence of many complex genetic diseases associated with a Western lifestyle and diet. During the last few decades, the prevalence in India of complex genetic diseases associated with increased life span and with urban and Western lifestyles, including coronary artery disease, non-insulin-dependent diabetes and metabolic syndrome, has risen considerably and is now greater than in most other populations. Although Indian populations constitute more than one-sixth of the world’s human population, they have not generally been incorporated into the largest genomic surveys and thus, a genome-wide catalogue of genetic variation important to the design of association studies does not yet exist for India.

Studies in India

In the Indian context, majority of the PCOS studies have been confined to the clinical dimensions. Apart from one genetic association study, no family studies regarding PCOS have been reported so far. Maitra et al. conducted mutational analysis of CYP11A1 and Leptin as genetic determinants of hyperandrogenicity and obesity in PCOS patients, although the study did not indicate any variations in the exons of the aforesaid genes with regard to the syndrome. The same group exhibited a trend towards dyslipidaemia among women with PCOS, particularly in parameters associated with cardiovascular risk. A significant association of obesity rather than raised testosterone with this dyslipidaemia was also confirmed by this study. In addition to this, Kalra et al. concluded that IR is associated with dyslipidaemia in women with PCOS, independent of obesity. Incidence of type-2 diabetes is quite high in India and this metabolic feature was taken into account by Zargar et al., where a higher prevalence of polycystic ovaries was found in women with T2DM as compared to non-diabetic subjects. Asian Indians are insulin-resistant and prone to metabolic syndrome at an earlier age. South Indian women with the reproductive abnormalities of PCOS have greater IR and inertial median thickness (IMT), and therefore they must be advised about lowering the risk of future vascular disease. IR is central to the pathogenesis of PCOS, while type-2 diabetes is commoner in South Asians. The prevalence of polycystic ovaries in Indian women is very high and it has significant clinical associations.
Polycystic ovary syndrome is a highly prevalent endocrine disorder affecting approximately 7% of women of reproductive age. Patients with PCOS have several interrelated characteristics including hyperandrogenism, altered gonadotropin dynamics, chronic anovulation, polycystic ovaries and IR. The syndrome has a significant reproductive and metabolic impact, and is associated with increased risk of type 2 diabetes, dyslipidaemia, cardiovascular disease (CVD) and endometrial carcinoma. Development of PCOS may require the interaction of multiple genetic and environmental factors. The metabolic syndrome is evident at an early age in women with PCOS, irrespective of race and ethnicity. Hyperinsulinaemia, a central factor in the pathogenesis of PCOS, also appears to be a critical link between PCOS and the metabolic syndrome. In the absence of a concrete molecular genetic explanation for susceptibility, perhaps the most convincing evidence in favour of a particular variant or gene contributing to a complex disease is in the replicability of its association with the condition in different backgrounds. However, with regard to PCOS, such findings have yet not been obtained. Since most of the positive association studies are case-control studies based on large sample sizes, emphasis of future studies should be on the study design and the sample size. Apart from the conventional candidate gene approaches, the genome-wide scans might be promising. Further, employing cDNA technology, which would shed light on the functional aspect of the candidate genes, and epigenetic dimensions to the studies may help in attaining better understanding of the molecular genetic etiology of PCOS.

Considering the unique Indian population structure with strictly defined endogamous and genetically homogenous populations, it is imperative that more studies of molecular genetic nature should be undertaken in order to elucidate the pathogenicity and effect of ethnicity on the manifestation of this syndrome paving way for suitable medical intervention.

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