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REVIEW ARTICLE

Genetics of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a syndrome involving defects in primary cellular control mechanisms that result in the expression of chronic anovulation and hyperandrogenism. This syndrome has been for many years one of the most controversial entities in gynecological endocrinology. Polycystic ovary syndrome has been proven to be a familial condition. Although the role of genetic factors in PCOS is strongly supported, the genes that are involved in the etiology of the syndrome have not been fully investigated until now, as well as the environmental contribution in their expression. The heterogeneity of the syndrome entertains the mystery around this condition which concerns thousands of infertile women worldwide. Some genes have shown altered expression suggesting that the genetic abnormality in PCOS affects signal transduction pathways controlling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation and others. The present review of the contemporary literature constitutes an effort to present all the trends in the current research for the etiology of polycystic ovary syndrome. Hippokratia 2009; 13 (4): 216-223

Key words: polycystic ovary syndrome, etiology of PCOS genetics of PCOS

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Polycystic Ovary Syndrome (PCOS) is a familial condition, as has long been noted[1,2]. Some clinical genetic studies have pointed to an autosomal dominant inheritance[1,3,4] while others showed that it was more likely that the syndrome is a complex trait with oligogenic basis[5,6]. Although 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. Modifications of molecular structure of gonadotrophins, their receptors and of the enzymes involved in steroidogenesis, insulin action and secretion have been under continuous and intense investigation with variable results. Whereas several positive results have been reported, there are no genes universally accepted fondamentally important in PCOS aetiology. This has resulted partially because of various factors such as the lack of a worldwide accepted diagnostic scheme for PCOS, diagnostic capability only in reproductive-aged women, limited number of patients in case-control studies, analysis of only one or two variants of candidate genes and incomplete knowledge of pathophysiology of the syndrome.

Two possible approaches are used to identify a genetic locus for PCOS genes: (i) association studies where a predisposing allele is expected to be found more frequently in the affected population than the normal individuals and (ii) linkage studies where the probands and their families are investigated to determine if particular genomic landmarks are distributed independently or in linkage with the phenotype. While the mode of inheritance is not required for the association studies, it requires a relatively large set of individuals for a clear conclusion[7]. Many genes presented altered expression suggesting thus that the genetic abnormality in PCOS affects signal transduction ruling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation and others.

Genes involved in ovarian and adrenal steroidogenesis

The first step in steroidogenesis is the conversion of cholesterol into progesterone, catalyzed by the P450 cytochrome side chain cleavage enzyme encoded by CYP11a gene located at 15q24[8]. Investigation of CYP11A gene showed a significant association between serum testosterone levels and the alleles of the CYP11a with a 5' untranslated region (UTR) consisting of repeats of a (tttta)n pentanucleotide, a variable number tandem repeat (VNTR) polymorphism[9]. Two other case-control studies[10,11], confirmed these findings in support of the encouraging evidence for the association between CYP11a and PCOS. However, subsequent studies[12,13] have failed to find any significant association between this gene locus and its VNTR alleles and PCOS. Further investigation is required due to these controversial results in order to confirm a role in the aetiology of PCOS of this gene.

Another part in steroidogenesis is the conversion of 17-hydroxyprogesterone into 11-deoxycortisol which

is catalyzed by the 21-hydroxylase enzyme encoded by CYP21. The deficiency of this enzyme is responsible for most cases of congenital adrenal hyperplasia and increased serum 17-hydroxyprogesterone levels are correlated with its deficiency. It is a common finding among women with functional hyperandrogenism or PCOS an increased serum 17-hydroxyprogesterone response to ACTH stimulation[14,15]. Furthermore, patients having both heterozygote CYP21 mutations and clinical symptoms exhibit a PCOS-like phenotype[16]. Accordingly, mutations of CYP21 have been investigated as a candidate gene in patients with PCOS. Two studies showed that children with premature pubarche and adolescent girls with hyperandrogenism were heterozygous for mutations in CYP21[16,17]. On the other hand, there are other researchers that found no clear concordance between the CYP21 genotype and the functional origin of androgen excess[18,19]. Overall, CYP21 and associated mutations do not seem to play a key role in the development of PCOS.

The conversion of pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and of these steroids into dehydrohepiandrosterone (DHEA) and Δ_4-Androstendione (Δ_4A) is catalyzed by the P450c17α enzyme. This enzyme has both 17α-hydroxylase and 17,20-lyase activities and is encoded by CYP17 located at 10q24.3[20]. It was reported increased P450c17α expression and enzymatic activity in ovarian theca cells from women with PCOS as well as increased transactivation of the CYP17 promoter[21-23]. Moreover, it was showed that CYP17 expression is dysregulated at the level of mRNA stability in PCOS theca cells[24]. Another study identified a rare T/C single nucleotide polymorphism (SNP) in the promoter region of CYP17 increasing the susceptibility to develop PCOS[25]. Subsequently, more comprehensive studies have failed to detect a significant linkage between CYP17 and PCOS[26-29]. Although CYP17 gene does not seem to be a candidate gene in the pathophysiology of PCOS, it should be noted that post-translational regulation of this gene product might play a role in the pathophysiology of PCOS[7].

The enzyme complex aromatase converts androgens to estrogens. This enzyme complex is composed of the cytochrome P450 aromatase and the NADPH cytochrome P450 reductase[30], and P450arom is encoded by CYP19 located at 15p21.1[31]. Aromatase deficiency has been reported in a number of hyperandrogenic patients[32,33]. It has been demonstrated that granulosa cells obtained from medium-sized follicles of women with PCOS have little aromatase activity[34]. Similarly, it has been showed that when compared to the control follicles, all PCOS follicles contained low levels of P450arom mRNA, estradiol, and lower aromatase stimulating bioactivity[35]. These findings indicate that the aromatase activity might be decreased in PCOS follicles, and that the possible androgen excess resulting might contribute to abnormal follicle development. Association studies utilizing SNPs and haplotypes showed association with PCOS symptoms and serum testosterone levels[36,37].

Genes involved in steroid hormone actions

All androgens transmit their signal through the androgen receptor which belongs to a family of nuclear transcription factors. The androgen receptor is encoded by the gene (AR) located at Xq11-12[38] and is composed of three functional domains: the transactivation domain, the DNA binding domain, and the ligand-binding domain. A VNTR polymorphism consisting of CAG repeats in exon-1 encoding a polyglutamine chain in the N-terminal transactivation domain is embedded in AR[39]. The transcriptional activity of androgen receptor is inversely correlated with the number of CAG repeats[40]. Variations of these repeats, even within the normal polymorphic range, have been related to various disorders associated with low- or high-androgenic activities[41-43]. Therefore, decreased number of CAG repeats with an increased androgen receptor activity could explain some of the PCOS phenotype exhibiting the normal serum androgen levels and hyperandrogenism symptoms[44]. Nevertheless, some studies failed to prove any association between this VNTR and PCOS[44,45]. On the contrary, other studies demonstrated a significantly greater frequency of alleles with longer CAG repeats for infertile PCOS patients compared with fertile women[46]. Concluding, AR gene is not a strong candidate for the etiology of PCOS.

Serum Sex Hormone-Binding Globulin (SHBG) levels are commonly low in patients with hyperandrogenism, especially in association with PCOS[47]. SHBG is composed of a homodimeric glycoprotein produced by hepatocytes and is encoded by a 4-kb gene at the 17p12-p13[48,49]. A pentanucleotide repeat polymorphism, at the promoter of SHBG gene has been described to influence the transcriptional activity of SHBG gene[50]. Consequently, it has been investigated whether this polymorphism is associated with PCOS and whether polymorphic variants of the gene are related to serum SHBG levels in women with PCOS[51]. A significant association was found between this polymorphism and PCOS[51]. PCOS patients carrying the longer allele genotypes had lower SHBG levels. In accordance with the latter result, Cousin et al.[52] recently demonstrated that longer alleles lowered serum SHBG levels in hirsute women when compared with six repeat alleles. Although Urbanek et al.[45] did not find any association or linkage between a marker close to the locus and PCOS, it could be concluded that SHBG gene is a potential candidate gene in the pathogenesis of PCOS[7].

Genes involved in gonadotropin action and regulation

The gene encoding the β-subunit of LH which is responsible for LH specificity, has been explored in PCOS patients[7]. Initially, it was identified an abnormal form of LH with two-point mutations, Trp8Arg and Ilg15Thr, in the LH β-subunit gene[53]. In addition, these mutations produced structural changes in the variant LH molecules (v-LH)[54] and caused v-LH to have an increased in vitro activity and a decreased in vivo half life compared to that of non mutant form[55]. However, in vivo activity of v-LH

could not be explained. The implication of v-LH in both healthy women and PCOS patients was explored and it was found that the occurrence of these mutations in LH β-subunit gene was not higher in PCOS compared with healthy women[7,56]. On the other hand, subgroup analysis of this study revealed that obese PCOS patients had a higher frequency of the heterozygous v-LH compared with obese controls[7,56]. However, other studies failed to find any association with PCOS[57-59]. The assumption that an activating mutation in the LH receptor gene could trigger hyperandrogenism in patients with PCOS having normal serum LH concentrations and high androgen levels was demolished[8]. Overall, the functional role of the v-LHs is unclear but it seems not to be crucial in PCOS pathogenesis or female infertility.

Follistatin, a monomeric glycoprotein encoded by a single gene, is linked functionally through its role as a high-affinity binding protein for activin[60]. Activin is dimeric glycoprotein which belongs to the TGF-β superfamily, induces FSH and insulin secretion, ovarian follicular maturation and inhibits LH-stimulated ovarian androgen production[60]. Actually, overexpression of follistatin in transgenic mice resulted in suppression of serum levels of FSH and arrested ovarian folliculogenesis[61]. Therefore overwhelming activin neutralization due to increased follistatin reduces FSH concentrations, arrests follicular maturation, augments androgen production, and impairs insulin release. Because all of these changes are typical features of PCOS[62], follistatin gene has been explored as a candidate gene in PCOS. The results of distinct studies are conflicting and significant linkage was failed to be proven[45,63,64].

Genes involved in insulin action and secretion

The insulin gene (INS) is located between the genes for tyrosine hydroxylase and for IGF-II at 11p15.5, and includes variable tandem repeats (VNTR) embedded at the 5'regulatory region of INS[65]. The VNTR polymorphism regulates the transcriptional rate of the INS[66] and probably that of the gene encoding IGF-II[67]. The number of the repeats of the INS VNTR ranges from 26 to 200, and due to this feature INS VNTR polymorphism has three size classes. Class-I alleles comprise the shorter polymorphism, consisting of a length of 40 repeats. Class-II alleles are composed usually of 80 repeats and are uncommon in Caucasian. Class-III alleles compose the longest polymorphic region having an average of 157 repeats[68]. Transcriptional activity of the longer polymorphic region is greater than that of the shorter one[66]. Besides their effect on regulating INS expression, they have been implicated in the pathogenesis of type-2 Diabetes Mellitus (DM) in many studies[69,70]. The hyperinsulinemia in PCOS may be the result of primary insulin resistance or the direct effect of pancreatic β-cell disorder as defects in both insulin action[71, 72] and in pancreatic β-cell function[73,74] have been reported. Therefore, it was evaluated the linkage and association of the INS VNTR polymorphisms in families with affected members with PCOS[75].

An association was found between PCOS and allelic variation at the INS VNTR locus in three separate populations[75]. Furthermore, it was found that class III alleles were associated with anovulatory PCOS in two independent populations and were more frequent among women with Polycystic Ovaries (PCO) with symptoms than those without symptoms[75]. In addition, it was shown that the fasting serum insulin levels were significantly higher in families with evidence of linkage[75].. This evidence stands for the assumption that VNTR polymorphisms affect the presence of hyperinsulinemia and insulin resistance in some PCOS phenotypes. It was also reported that class III alleles were transmitted significantly more common from fathers than from mothers to affected daughter suggesting a "parent of origin" effect[75, 76]. In support of this evidence, it was demonstrated that class III alleles and paternal class III allele transmissions were significantly related to increased number of PCOS features and to reduced insulin sensitivity among women with PCOS[77]. In other studies, however, it was not found any evidence for the linkage of INS and PCOS and for the association of the class III allele and of hyperandrogenemia[78,79]. But there was a difference in these studies. The ultrasonographic criteria were more commonly used than the NIHCD criteria. These conflicting results may be explained by the variant selection criteria, the different ethnic and geographic distribution of studied patients, the selection bias and the small size of the samples.

The insulin receptor is a heterotetrameric glycoprotein comprised of two α and two β-subunits and is encoded by the insulin receptor gene (INSR) located at the chromosome 19[80]. Many researchers have tried to explore whether the mutations of INSR could explain insulin resistance in PCOS. The first studies of sequencing the INSR, the tyrosine kinase domain of INSR and the mutations by molecular scanning of the entire coding region of INS did not reveal any mutations[81-83]. More recently, a comprehensive study published by Urbanek et al.[84] demonstrated a linkage with PCOS 367 well-characterized families from Europe. Another study investigating a broad region of the chromosome 19p13.2 found strong evidence for association with D19S884, supporting thus the previous findings[84]. In a recent study, Siegel et al.[85]. examined an SNP at the tyrosine kinase domain of INSR and found an association in lean patients with PCOS. This SNP could be a susceptible variant for PCOS, or a result of linkage disequilibrium with another INSR polymorphism.

The activation of the insulin receptor after insulin binding requires the autophosphorylation of the β-subunit of the insulin receptor[86]. The following tyrosine kinase activity produced after autophosphorylation phosphorylates insulin receptor substrates (IRS), such as IRS-1 and IRS-2[87]. Then, IRS-1 and IRS-2 bind and activate downstream effectors, such as phosphoinositide 3-kinase, to promote the metabolic and mitogenic actions of insulin. When IRS-1 is dysfunctional, IRS-2 is

the main messenger for the intracellular transmission of the insulin signal but it demands higher insulin concentration for activation[88]. Several polymorphisms of IRS1 and IRS2 genes (IRS1and IRS2) have been implicated in insulin resistance. The Gly972Arg polymorphism for IRS-1 and Gly1057Asp for IRS-2 have been shown to increase susceptibility to type-2 diabetes mellitus[89,90]. Initially, no difference could be found in the distribution of IRS-1 Gly972Arg and IRS-2 Gly1057Asp alleles in PCOS patients and controls[45, 91]; however, it was demonstrated that the Gly972Arg IRS-1 was more prevalent in insulin-resistant patients compared with the non-insulin resistant patients or controls. Many studies following failed to prove any strong relationship or confirmation of any possible correlation between polymorphisms of IRS-1 and IRS-2 and PCOS[91-93].

In a recent study Dilek et al.[94] reported a higher frequency of the Gly972Arg polymorphism for IRS-1 in women with PCOS. Furthermore, similar to previous studies[91,93] they found that the Gly972Arg carriers were more obese, more insulin-resistant and had higher fasting insulin levels in comparison to other PCOS patients and controls[94]. These investigators also studied the same PCOS patients for the potential differential effects of metformin therapy on the basis of IRS-1 genotype[95]. Metformin administration resulted in lower LH, DHEAS, T, and fasting insulin levels and decreased insulin resistance and FAI in Gly972Arg-negative PCOS women more effectively and significantly when compared with the Gly972Arg-positive women[95]. These findings could be considered a rough indicator of the relationship between the IRS-1 genotype and the insulin resistance phenotype of PCOS. Ertunc et al.[95] studied the hypothesis that a possible mechanism for the action of metformin may be augmentation of the tyrosine phosphorylation of the insulin receptor β-subunit and IRS proteins and the increase of the insulin-dependent and nondependent cellular glucose uptake through the family of glucose transporter proteins. They hypothesized that variant IRS-1 proteins could not transmit signals in order to increase the glucose uptake of muscle and adipose cells. This may be an explanation of the association of IRS-1 genotype with insulin resistance in some of PCOS patients. The IRS polymorphisms of these studies seem to be related mostly with insulin resistance rather than PCOS.

Calpain-10 is a cysteine protease that participates in insulin secretion and action[96], and genetic studies have shown that variation in the gene (CAPN10) encoding calpain-10 is associated with type-2 diabetes[97]. There was an effort to determine whether variation in the CAPN10 is associated with quantitative traits related to the pathogenesis of PCOS and type-2 diabetes[98]. It was found association between the 112/121 haplotype of this gene and higher insulin levels in African-American women and an increased risk of PCOS in both African-American and white women[7,98]. Consecutive studies have had conflicting results about the relation of polymorphisms with PCOS[99-101].

Genes involved in energy homeostasis

During the last years it has been recognized that the adipose tissue is not only a connective tissue but is also one of the active endocrine organs which secretes a wide variety of products called adipocytokines[102]. As a large proportion of women with PCOS are overweight, obese and extremely obese some genes of the most popular adipocytokines have been investigated as candidate genes in the pathogenesis of PCOS. Sequencing the leptin gene in a small group of PCOS patients failed to detect any mutations of the coding exons[103]. In this study, the leptin receptor gene was also sequenced and revealed previously identified amino acid variants in exons 2, 4, 12 and the pentanucleotide insertion in the 3'-untranslated region[103]. However, the allele frequencies of these polymorphisms did not differ from those in the general population.

Recent studies have focused on two polymorphisms, T45G in exon 2 and G276T in intron 2. It was demonstrated that these polymorphisms associate with obesity, insulin resistance, and the risk of developing type-2 diabetes[104-106]. In a study investigating the relationship of PCOS with 15 genomic variants previously described to influence insulin resistance, obesity, and type-2 diabetes mellitus, there was no association between PCOS and these two common polymorphisms of the adiponectin gene[107]. Panidis et al. investigated the possible association of the T45G adiponectin gene polymorphisms with PCOS[108]. A significant difference was observed between the groups when genotypes GG and TG were assessed together[109]. It was also showed that the carriers of the G allele had a tendency for lower serum adiponectin levels in PCOS group[109]. More recently, the probability that the T45G and G276T polymorphisms of adiponectin gene could be associated with PCOS was disputed by two studies[109, 110]. Concluding, the adiponectin gene do not seem to play a causative role in the pathogenesis of PCOS, rather seem to reflect the severity of the syndrome, at least concerning the metabolic disturbances and to have a role in the phenotypic variability of PCOS.

Genes involved in chronic inflammation

Tumor necrosis factor (TNF)-α is a cytokine secreted by adipose tissue with an important role in insulin resistance[111]. The polymorphisms in the TNF-α gene do not seem to have a key role in the etiology of PCOS. In one study the carriers of the mutation 308 A alleles showed increased androgen and 17-hydroxyprogesterone levels before and after GnRH stimulation[112]. These data may be indicative of the hypothesis that TNF-α gene polymorphism might be a modifying factor for phenotypic features. Other genes involved in chronic inflammation, such as TNFR2 (type-2 TNF receptor) gene[113], IL-6[114], IL-6 signal transducer gp 130[115], IL-6 receptor[115] genes have also been investigated for association with PCOS, but without significant results.

Abnormalities in the coagulation and fibrinolytic pathways contribute to the development of cardiovascular disease in PCOS patients[116]. Elevated plasminogen

activator inhibitor-1 (PAI-1) levels are associated with increased cardiovascular risk and increased thrombogenic tendency. Women with PCOS also present an increased activity of PAI-1[117]. In order to investigate the role of the PAI-1 polymorphism in PCOS patients, the polymorphism 4G/5G which is associated with higher PAI-1 concentrations, was evaluated in Greek women with PCOS and it was found a higher frequency in PCOS women compared with controls[118]. It was also reported that PCOS women have higher levels of PAI-1 and that the presence of the 4G allele in the PAI-1 promoter region of the gene further increases the PAI-1 levels[118].

In addition to the genes mentioned above, many different genes such as HSD3B2[119], 17α-hydroxysteroid dehydrogenases[120], dopamine receptor[121,122], IGF[107], aldosterone synthetase[123], paraoxonase[123], glycogen synthetase[124], resistin[125], apoprotein E[126] have been studied. Results were either controversial or without clear conclusions.

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