Genetics of polycystic ovary syndrome: searching for the way out of the labyrinth

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Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disorder presenting a challenge for clinical investigators. It is the most common endocrine disorder of women in reproductive age, a multifaceted reproductive, cosmetic and metabolic problem, with an enigmatic pathophysiological and molecular basis. Although the familial segregation has been noticed very early in the description of the syndrome and family studies in first-degree relatives of women diagnosed with PCOS reveal clustering of the disease, the genetic studies have not as yet determine the pattern of heredity. Part of the problem in genetic studies has been the lack of uniform criteria for diagnosis, heterogeneity of phenotypic features and the fact that the disorder is only expressed clinically in women during their reproductive years. Even within affected families and between sisters with polycystic ovaries, there is heterogeneity in presentation. However, regardless of diagnostic criteria used to identify profanes and to determine affected status in the kindred, the foundation of genetic studies suggests a strong familial component. Currently, PCOS is considered a polygenic trait that might result from the interaction of susceptible and protective genomic variants under the influence of environmental factors, whose role is under intensive investigation. Candidate genes cover a broad spectrum of an endless list of molecules which participate on every step of reproductive and metabolic pathways of this syndrome. Focused research in identification of these genes may provide valuable information and shed some light on the way out of the genomic labyrinth, elucidating the underlying pathophysiology and aiming at a more efficient therapeutic approach of this complicated endocrine disorder.

Key words: candidate genes/environmental factors/metabolic abnormalities/molecular factors/PCOS

Definition, clinical picture and epidemiology of polycystic ovary syndrome

The definition of polycystic ovary syndrome (PCOS) has been an issue of great and continuous debate, among experts in the field. The 1990 National Institutes of Health-sponsored conference (NIH) on PCOS put forward the first diagnostic criteria of chronic anovulation and hyperandrogenemia. Since then it has been widely appreciated that the syndrome encompassed a broader spectrum of symptoms and signs than those originally defined and that no single diagnostic criterion is sufficient for its clinical diagnosis. Furthermore, it is established knowledge that PCOS is a very heterogeneous and complex syndrome and cannot be diagnosed on one imaging technique, a point well illustrated by previous studies based on such criteria which present a prevalence range from 65 to 87% in women with oligoanovulation and hyperandrogenemia. Since then it has been widely appreciated that the syndrome encompassed a broader spectrum of symptoms and signs than those originally defined and that no single diagnostic criterion is sufficient for its clinical diagnosis. Furthermore, it is established knowledge that PCOS is a very heterogeneous and complex syndrome and cannot be diagnosed on one imaging technique, a point well illustrated by previous studies based on such criteria which present a prevalence range from 65 to 87% in women with oligoanovulation and hyperandrogenemia. O’Driscoll et al., 1994). More recent European and American studies using NIH criteria are in agreement that PCOS should include two of the following three criteria: (i) oligo- and/or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism and (iii) polycystic ovaries on ultrasonography and exclusion of related disorders. The syndrome is widely accepted as the commonest cause of anovulatory infertility with clinical and/or biochemical signs of excess androgen secretion, associated with hyperinsulinemia and high prevalence of significant metabolic abnormalities, with long-term sequelae which may affect the women’s long-term health (Fauser et al., 1991; Diamanti-Kandarakis, 1997; Dunaif, 1997; Nestler, 1997a; Azziz et al., 1998; Tsilchorozidou et al., 2004).

A recent experts meeting in Rotterdam in 2003 sponsored by European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (Rotterdam, ESHRE, ASRM, 2004) suggested that the definition of PCOS should include two of the following three criteria: (i) oligo- and/or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism and (iii) polycystic ovaries on ultrasonography and exclusion of related disorders. The syndrome is widely accepted as the commonest cause of anovulatory infertility with clinical and/or biochemical signs of excess androgen secretion, associated with hyperinsulinemia and high prevalence of significant metabolic abnormalities, with long-term sequelae which may affect the women’s long-term health (Fauser et al., 1991; Diamanti-Kandarakis, 1997; Dunaif, 1997; Nestler, 1997a; Azziz et al., 1998; Tsilchorozidou et al., 2004).

The signs and symptoms of PCOS usually appear during or close to the onset of puberty (Ibanez et al., 1994; Balen et al.,
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1995), and signs of precocious pubarche as well as adolescent hyperandrogenemia with or without insulin resistance may be manifested at early stages of the syndrome.

Furthermore, the phenotype may change through the life cycle of the woman, making the clinical picture very unpredictable and escaping the diagnosis at some point throughout the woman’s life. Interestingly the nature of male phenotype remains controversial, with premature balding however, being considered as the more prevalent phenotype but this has only been confirmed by some of the investigators.

**Pathogenetic mechanisms in polycystic ovary syndrome: a brief overview**

The pathophysiology of the syndrome of polycystic ovaries is polyprismatic and analysis of the spectrum of phenotypes from a single angle of pathogenetic view cannot adequately interpret it. Genetic and environmental factors are interconnected and currently we continue identifying risk factors causing multiple aberrations in steroidogenesis, folliculogenesis and metabolic pathways without being able to determine which the key abnormality is.

**Environmental risk factors: obesity and diet**

Undoubtedly environmental factors, interacting with a PCOS genetic background, could affect the two major components of the syndrome, hyperandrogenemic anovulation and insulin resistance, since androgenized animals present increased adipsity (Abbott et al., 2002) and obesity is an independent risk factor of anovulation (Grodstein et al., 1994).

Oligoovulation is associated with increased adiposity and concomitant hyperinsulinemia. Subsequently, hyperinsulinemia with increased levels of LH has an additive negative effect on preovulatory follicles, terminating the differentiation of granulosa cells (GC) and causing premature cessation of ovulatory process (Franks et al., 1998; Jonard and Dewailly, 2004).

There are interesting findings among PCOS sisters revealing the role of obesity. Body weight differs between the phenotypes in affected PCOS sisters (Legro et al., 1998). Sisters with irregular cycles and hyperandrogenemia are heavier than sisters with regular cycles and hyperandrogenemia, whereas unaffected sisters have lower body weights than the affected ones (Legro et al., 2002). The study by Taylor et al. (2002) showed that normal weight women with PCOS eat less than normal women of similar body weight. Retrospective studies suggest that different intrauterine environment is linked to different PCOS phenotypes like PCOS women with increased birth weight and those born from overweight mothers (Cresswell et al., 1997).

Interestingly not only the quantity of food but the type of nutrition and the type of nutrition as well may alter PCOS phenotype, possibly interacting with different genetic patterns.

Carmina et al. (2003) demonstrated that women with PCOS from Sicily are less obese than women from Pennsylvania and that body mass was significantly higher in US women with PCOS compared with Italian women. However, total calorie intake and dietary constituents were similar, except from higher saturated fat content in diet of US women. Therefore, it was hypothesized that diet alone does not explain differences in body mass, since their food differed only in the quality of consumed fats and not in quantity. From these data, it was concluded that genetic and lifestyle factors contribute to body weight differences.

A recent study from our group showed that non-obese, normoglycemic PCOS women compared to matched controls had higher levels of glycotoxins, advanced glycation end products (AGEs), which were positively correlated with insulin resistance indices and hyperandrogenemia (Diamanti-Kandarakis et al., 2005).

These glycotoxins, known to be associated with increased risk of atherosclerosis, are produced endogenously but are also found abundant in fast-food meals, and it has been shown that they are absorbed from exogenous sources (Koschinsky et al., 1997).

Food quality seems to play more active role in metabolic abnormalities and could interfere in reproductive dysfunction in PCOS directly or indirectly.

**Molecular factors**

**Abnormalities in ovarian steroidogenesis and folliculogenesis**

The ovary remains the primary source of hyperandrogenism in PCOS. Intraovarian androgen biosynthesis is under tight control. It could be said that androgens represent the ‘necessary evil’ in the ovary, since from the one hand they are the essential substrate for estrogens production but on the other hand their excess seems to interfere in the selection process of the principal ovarian follicle. Consequently, intraovarian androgens concentration has to remain in specific limits, during different stages of follicular maturation, tunable to the ancient Greek explicit ‘meden agan’ (*not too much of anything*).

Animal models like the prenatally androgenized female rhesus monkey provide a unique nonhuman primate model for PCOS and exhibit oligoovulation, multifollicular ovaries, elevated LH and increased upper abdominal obesity predisposing to insulin resistance (Abbott et al., 2002; Zeleznik et al., 2002). In these experimental studies, oligoovulation and hyperinsulinemia was more prevalent in obese animals compared to lean ones, demonstrating a significant positive correlation between BMI and fasting insulin levels. Moreover, these androgenized animals had also increased skin fold thickness which is strongly correlated with abdominal obesity, which in turn exhibits decreased antilipolytic action of insulin, leading to elevated free fatty acid (FFAs) finally resulting in insulin resistance. In this very important in vivo experiment, the interplay between the presence of excess of androgens with hyperinsulinemia and abnormalities in fertility is demonstrated. Interestingly, hyperinsulinemia is associated with elevated levels of LH, where their combined action could affect maturing follicles contributing to oligoovulation with formation of enlarged multifollicular ovaries. Furthermore, the arrested follicles in these animals, are reminiscent of the increased medium-sized follicles found in the ovaries of PCOS women.

Catheterization studies of ovarian vein, suppression studies of ovarian function and stimulation of ovarian steroidogenesis with GnRH have clearly demonstrated the source of androgen in PCOS (Barnes and Rosenfield, 1989; Barnes et al., 1989, 1998). Androgen biosynthesis in the human ovary takes place primarily in theca interstitial cells (TIC), whose activity is excessive in PCOS. The ovarian hyperandrogenism is a result of increased activity throughout the thecal cell steroid production pathway (Gilling-Smith et al., 1994). This increased activity of thecal cell
steroid production is intrinsic to the thecal cell because it persists after multiple passages of thecal cell cultures in vitro (Nelson et al., 1999). Ovarian theca cells propagated from patients with PCOS convert steroid precursors into testosterone (T) more efficiently than normal theca cells. The rate of conversion of pregnenolone (P) and dehydroepiandrosterone (DHEA) into T was markedly increased in PCOS theca cells. Furthermore, the 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme activity was unaffected and 20α-HSD enzyme activity is increased only about 75% in PCOS theca cells. In contrast, 17α-hydroxylase/C17,20 lyase and 3-HSD enzyme activities were elevated in PCOS theca cells, driving increased production of T precursors. These findings indicate that increased T production in PCOS theca cells does not result from deregulation of ‘androgenic’ 17-HSD activity but the primary factor driving enhanced T secretion in PCOS is increased synthesis of its precursors (Nelson et al., 2001). These data should also be interpreted in the light of recent findings, Wood et al. (2003) who found increased mRNA abundance in PCOS TIC corresponding to the genes of aldehyde dehydrogenase-6 and retinol dehydrogenase-2, by which both increase the expression of 17α-hydroxylase. The above data suggest that there are several defects in thecal cell steroidogenesis and it is unlikely that the hyperandrogenaemia of PCOS is principally determined by molecular or genetic defects in a single steroidogenic enzyme activity (Gharani et al., 1997; Diamanti-Kandarakis et al., 1999b, 2000; Urbanek et al., 1999; Strauss et al., 2002; San Millan et al., 2001).

Although theca cell dysfunction seems to be the main defect of intraovarian hyperandrogenism, granulosa cell deregulation may also play a role, via regulatory factors secreted from GC. Ovarian GC produce inhibins which are thought to modulate directly follicular steroidogenesis. Hillier et al. (1991) showed that recombinant inhibin A enhances both basal and LH-induced androgen production by cultured human TIC. Thus, inhibins might be involved in the excess of intraovarian androgens in PCOS through a paracrine effect from GC (Magoffin and Weitsman, 1994; Udoff and Adashi, 1995).

The earliest follicular abnormality in PCOS is an increased number of early-growing and selectable follicles, in which intraovarian hyperandrogenism is involved. Recent data have shown that overproduction of antimitogenic factor (AMH) from GC in PCOS (Cook et al., 2002; De Vet et al., 2002; Piginy et al., 2003; Joop et al., 2004) could be implicated in hyperandrogenism, since a positive correlation has been found between AMH, T and androstenedione in PCOS but not in controls (Fancin et al., 2002, 2003; Piginy et al., 2003). These findings could well be linked with a paracrine action of AMH on theca cell’s over activity by the demonstration of the AMH type II receptor (AMHRII) in TIC of maturing follicles (Ingraham et al., 2000). Another factor, although still controversial, which has also been implicated in hyperandrogenemia, basal or LH stimulated, is the GDF-9 (Di Clemente et al., 1994; Solovyeva et al., 2000). Supportive data come from in vivo studies, in intact monkeys, demonstrating that androgen treatment increases the number of pre-antral and small antral follicles up to 1 mm in diameter, by acting through androgen receptors (Dewailly, 1997; Hillier and Tetsuka, 1997; Vendola et al., 1998). The role of androgen excess signifies their close relationship with the accumulation of 2–5 mm follicles, which gives the typical aspect of multifollicular ovaries at ultrasonography (Takayama et al., 1996; Jonard and Dewailly, 2004).

In PCOS, there are an increased number of the recruited ovarian follicles with clearly abnormal growth, typically arrested at a diameter of 4–8 mm, indicating an abnormal endocrine environment, but it is not clear whether this is due to an intrinsic abnormality in ovarian folliculogenesis. Accumulating data suggest that intraovarian androgen excess interacts with the recruitment process of large numbers of small preovulatory follicles, which fail to respond to normal concentrations of FSH, instead of the emergence of a single dominant follicle. The second major abnormality in the folliculogenesis which may explain the anovulation of PCOS is the manifestation of follicular arrest in which the selection of the dominant follicle is impaired, despite the excess in the number of selectable follicles. Interestingly, early exposure of GC in LH inhibits their proliferation in a way that the development of the dominant ovarian follicle is interrupted.

A common feature in PCOS is an overall increase in plasma LH concentrations, consisting of both increased LH pulse frequency and LH pulse amplitude (Taylor et al., 2002). The resulting elevated serum LH concentration promotes ovarian TIC steroidogenesis (Gilling-Smith et al., 1994). The mechanism for the LH hypersecretion remains unclear, but fewer workers now consider it to be a primitive phenomenon. Recent data suggest that it results from an impaired negative feedback on LH secretion, because of excessive androgen action on the hypothalamic-pituitary axis (Eagleson et al., 2000). In addition, when patients with PCOS were given fixed dose of HCG, they showed hyperresponses of 17-hydroxyprogesterone and androstenedione (Δ4A) (Lanzone et al., 1990). Furthermore, patients with PCOS underwent regulation of their LH abnormality, through a 1-month treatment with GnRH agonist; they continued to exhibit 17-hydroxyprogesterone and androstenedione (Δ4A) (Lanzone et al., 1990). The role of androgen excess signifies their close relationship with the accumulation of 2–5 mm follicles, which gives the typical aspect of multifollicular ovaries at ultrasonography (Takayama et al., 1996; Jonard and Dewailly, 2004).

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Abnormalities in metabolic pathways

The role of hyperinsulinemia and insulin resistance was established on reproductive and metabolic aspects of the syndrome by pioneering studies of several outstanding investigators (Burghen et al., 1980; Dunai et al., 1987; Nestler et al., 1987, 1989; Reaven, 1988; Azziz et al., 1998; Ehrman et al., 1999; Legro et al., 1999). Women with this syndrome have elevated fasting and glucose stimulated insulin levels and inappropriately reduced insulin sensitivity for age and body weight matched healthy women. The aetiology of this metabolic abnormality is still under investigation, but clinical and molecular studies focused on insulin receptor and postreceptor defects shed some light to the mechanisms involved. There are elegant studies demonstrating impairment of intracellular signal transduction of insulin message. Dunai et al. (2001) have shown that the classic PCOS syndrome is determined by a distinct form of insulin resistance (Dunai, 1997); however, this molecular defect is not universally present. In PCOS, increased insulin levels are incriminated for direct stimulation of ovarian androgens’ production by means of the favourable action of this hormone to 17α-hydroxylase and to 17,20 lyase (cytochrome P450c17α) and in cytochrome P450sc (Poretsky and Kalin, 1987; Nestler and Strauss, 1991; Bergh et al., 1993;
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Hyperinsulinaemia provides another determinant of hyperandrogenism by enhancing the effects of LH on TIC steroid production, as extensively has been reported in the literature. The final outcome of this intraovarian hostile interaction, it seems to result in arresting the follicular maturation process (Hillier and Tetsuka, 1997; Franks et al., 1998).

Clearly, in PCOS there are environmental factors and molecular defects involved. Genetic studies using new molecular techniques as well as genetic analysis of PCOS families, searching the genes network, contribute significantly to the unfinished story of the PCOS pathogenesis.

The genetic spectrum of polycystic ovary syndrome

The spectrum of evidence for PCOS genetic basis is very broad supporting the molecular basis of this abnormality but by no means is adequate to interpret the pathogenesis of the syndrome.

Molecular defects in gonadotrophins and their receptors, in enzymes involved in steroidogenesis, as well as those underlying insulin action and secretion pathways, have been under continuous and intense investigation with variable results. Although this scientific race is quite stimulatory, it has not been possible to establish firmly the role of any particular gene or region, and it has not so far helped us to get in any way closer to the exit of this genomic labyrinth, or at least we are not aware of it as yet.

Furthermore, since the list of candidate genes is steadily increasing, major problems arise, whereas the findings are not confirmed between studies, in fact, there is difficulty even in replicating individual results. In addition, the constantly expanding spectrum of new candidates makes the focus less clear. Our current view, supports the notion that PCOS is likely to represent a complex oligogenic trait with multiple genetic defects (Franks et al., 1997, 2001; Urbanek et al., 1999; 2003). Before we enter the analysis of the current literature on each one of the contributory or ‘suspect’ genes, the methodology will be reviewed very briefly.

The methodology

Different approaches have been applied to elucidate the complex polygenic origin of PCOS such as family-based studies where linkage analysis aims to demonstrate co-segregation of a particular genetic variant or locus with a disease or trait, within families with consistent with an autosomal dominant or X-linked pattern of inheritance, using ultrasound scan for the diagnosis of PCOS, a method not universally accepted (Lunde et al., 1989; Franks et al., 1997).

The first genetic study was by Cooper et al. (1968), which studied 18 patients with Stein–Leventhal syndrome. Oligomenorrhea, hirsutism, and enlarged ovaries were much more common in sisters of cases than in sisters of controls. In the 1970s, Givens et al. (1971) using as diagnostic criteria hirsutism and either polycystic or bilaterally enlarged ovaries published reports indicating that PCOS could be inherited in an X-linked dominant fashion. In the first report, two families were described in which multiple individuals in more than two generations were affected. In one kindred, affected females experienced myocardial infarction in their fifth decade; and acanthosis nigricans, insulin resistance, and hypertension were present in many family members.

In third kindred (Cohen et al., 1975), several males showed maturational arrest of spermatogenesis. Excluding index cases, Wilroy et al. (1975) showed that 47% of female offspring of affected populations are not matched for ethnic background (so called population stratification). TDT also offers the prospect of assessing ‘parent of origin’ effects wherein there is preferential transmission of disease alleles from either the mother or the father to the affected offspring.

Linkage analyses on the other hand depend on the fact that polymorphic markers within, or closely linked to, a disease-susceptibility locus should show a tendency to segregate with the disease in families. A number of computer-assisted methods are available for linkage analysis. Traditionally, parametric logarithm of the odds ratio (LOD)-score based analytical methods has been used when there is clear evidence to support a particular mode of inheritance. On the other hand, nonparametric method of analysis (NPL) requires no assumption to be made about the mode of inheritance (e.g. the GENEHUNTER program) (He et al., 1999).

The identification of the gene or genomic variant underlying the association of the disease or trait with particular chromosomal region identified by linkage analysis requires positional cloning. The performance of linkage analysis depends heavily on the availability of relatively large, informative families.

Another approach is the use of association studies that detect co-occurrence of disease and genetic variation in specific candidate genes in unrelated cases and controls. Case–control studies are prone to false-negative findings when small samples sizes are applied, because large sample numbers are needed to reach statistical power in order to detect small gene defects usually contributing to complex medical syndromes.

Finally, the use of DNA microarrays for comparing genomic DNA variation or gene expression profiles in different target tissues of affected and unaffected individuals is a relatively new technique that may help to identify therapeutic targets.
females were affected. Among the offspring of males with an elevated LH/FSH ratio, 89% of daughters were affected. The fact that almost all daughters of affected males were affected is consistent with X-linked dominant inheritance.

In the UK, Ferriman and Purdie (1979) studied 381 patients with hirsutism and/or oligomenorrhea and a control group of 179 women. The interesting finding was that first-degree relatives with hirsutism and enlarged ovaries had a greater incidence of oligomenorrhea and infertility compared to first-degree relatives with normal sized ovaries and the control group.

Later British studies provided additional data in support of heritability of PCOS, specifically autosomal dominant inheritance. The significant role in genetic studies of diagnostic criteria was clearly shown by the study of Hague et al. (1988) which used ultrasound criteria and either hyperandrogenemia or LH hypersecretion to determine the frequency of PCOS in relatives of affected cases. PCOS was found in 45 of 52 (87%) of sisters of probands and in 24 of 36 (67%) of mothers. In this study, the frequency of affected relatives was dramatically higher than the 50% predicted for either autosomal dominant or X-linked dominant inheritance. Non-Mendelian mechanisms would need to be invoked in order to account for such a distorted segregation ratio. More likely, criteria were overly sensitive, leading to diagnosis false positivity.

Lunde et al. also conducted family studies in Norway in 1989 using hirsutism and oligomenorrhea as inclusion criteria. They found only 6–15% of first-degree relatives affected. Norman et al. (1996) found that, in 15 probands, far more relatives were affected. Among sisters, 11 of 15 (73%) had polycystic ovaries by ultrasound, 13 of 15 (87%) had elevated T and 10 of 15 (66%) hyperinsulinemia.

In the USA, Legro et al. (1998) studied 80 probands diagnosed on the basis of elevated T associated with oligomenorrhea (<6 menses/year); nonclassical 21-hydroxylase deficiency was excluded. They found 36 of 80 (45%) sisters to be affected on the basis of hyperandrogenemia.

A recent study by our group on phenotypically healthy sisters of women with PCOS showed evidence of insulin resistance. These women had neither clinical nor laboratory evidence of hyperandrogenism suggesting that insulin resistance is a dominant trait among PCOS families (Diamanti-Kandarakis et al., 2004a).

Govind et al. (1999) studied 29 probands and 10 control women. Diagnostic criteria consisted of polycystic ovaries on ultrasound with or without clinical or biochemical features of PCOS; 61% of female first-degree relatives were affected, and 22% of male first-degree relatives had early onset (before age 30) male-pattern baldness. The prevalence was much higher than in the control families. Of a total of 71 sibs of PCOS probands, 39 (55%) were affected, which is consistent with autosomal dominant inheritance. Kahsar-Miller et al. (2001) considered the frequencies of oligomenorrhea and either hirsutism or elevated T among first-degree female relatives within families of 93 probands with PCOS. A significantly higher rate of PCOS was observed among first-degree relatives than in the general population, suggesting genetic component in the disorder. However, several studies were performed which despite the fact that certain criteria were set, none led to adequate determination of the pattern of inheritance.

The most recent study by Ward et al. (2004), who used a large genealogy database to search for a founder effect and to evaluate the degree of heritability in PCOS, showed that the degree of relatedness among a PCOS population was four-fold greater than the average degree of relatedness among a large random sampling of the same database. A result, which just confirms the observation of the very first study showing that in PCOS there, is a family trait. Furthermore, it seems that studies, which included the PCOS morphology in the diagnostic criteria, favour the autosomal dominant pattern of inheritability as opposed to those that have not included it (Govind et al., 1999).

**Candidate genes**

A number of genes show altered patterns of expression suggesting that the genetic abnormality in PCOS affects signal transduction pathways controlling the expression of a family of genes, rather than the abnormal expression of a single gene. Consistent with this, cytogenetic studies have failed to identify common karyotypic abnormalities.

Clinical features of steroidogenic abnormalities are a cardinal characteristic in PCOS and investigators have long sought linkage or associations between PCOS and the various genes involved in the androgen biosynthetic pathway. On the other hand, the last 10 years numerous studies have confirmed the central role of insulin action in the pathogenesis of the syndrome. Subsequent genetic studies on insulin resistance with the associated metabolic aberrations included genes involved in chronic inflammation (Table I). A number of linkage and association studies of candidate genes in PCOS have yielded positive and/or mixed results, which are discussed below.

**Candidate genes involved in steroidogenesis**

The most common biochemical abnormality in women with PCOS is hypersecretion of androgens. The increased steroidogenic activity is due to increased 3α-HSD and 17α-hydroxylase/17,20-lyase activities (Nelson et al., 1999; Nelson et al., 2001). Northern blot analysis revealed that cytochrome P450 17-hydroxylase/17,20-desmolase (CYP17) and cytochrome P450 side chain cleavage enzyme (CYP11A) mRNAs were more abundant in PCOS theca cells than in normal ones. In addition, transient transfection experiments indicated that the CYP17 promoter is enhanced in PCOS theca cells compared to normal theca cells (Wickenheisser et al., 2000). The up-regulation of steroidogenesis in PCOS theca cells suggests the presence of an intrinsic defect in the metabolic pathways of the cells responsible for androgen production independently of environmental and neuroregulatory factors. However, theca cell studies have been performed only on classical PCOS phenotype with hyperandrogenemia and there is no information if all subtypes of theca cells present a steroidogenic defect. Additional studies on theca cells isolated from different PCOS phenotypes will provide valuable information.

**LH and its receptor.** A recent multicenter study investigating polymorphism in the LH b gene showed some interesting variations between populations but failed to find a clear causal link with PCOS (Tapanainen et al., 1999). Another study tested the hypothesis that an activating mutation in the LH receptor gene may be a cause of hyperandrogenism in PCOS, particularly in those subjects with normal serum LH concentrations and raised androgen levels (Lamminen and Huhtaniemi, 2001). Five families were identified in whom polymorphic markers close to the LH
## Table I. Candidate genes investigated for their possible association with polycystic ovary syndrome (PCOS)

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<td><strong>Genes involved in biosynthesis and metabolism of androgens</strong></td>
<td>LH and its receptor</td>
<td>Multicentric study, mutation of LH receptor, no linkage or association</td>
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<td>CYP11α- cytochrome P450 side chain cleavage enzyme</td>
<td>Randomized clinical study, partial association</td>
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<td>CYP17- cytochrome P450 17α hydroxylase/17,20 lyase</td>
<td>No association or linkage</td>
<td>Carey et al. (1994), Witchel et al. (1998), Diamanti-Kandarakis et al. (1999b)</td>
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<td>CYP21-cytochrome P450 21-hydroxylase</td>
<td>Mutation, no association</td>
<td>Escobar-Moreale et al. (1999), Witchel and Aston (2000)</td>
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<td>Androgen receptor</td>
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<td><strong>Genes involved in the secretion and action of insulin</strong></td>
<td>Insulin gene VNTR</td>
<td>Family study, no association</td>
<td>Urbanek et al. (1999)</td>
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<td>Family study, no association or linkage with PCOS</td>
<td>Bennett et al. (1995), Waterworth et al. (1997), Urbanek et al. (1999), Calvo et al. (2002), Vankova et al. (2002)</td>
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<td>Insulin receptor gene</td>
<td>Polymorphism in the tyrosine kinase domain of INSR showed association with PCOS. Caucaussian family studies, D19S884 marker near insulin receptor gene, chromosome 19p13.3 showed linkage and association</td>
<td>Dunai et al. (1995), Moran et al. (2001), Tucci et al. (2001), Siegel et al. (2002), Ukkola et al. (2002)</td>
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<td>Polymorphisms in IRS1 and IRS2, no association</td>
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<td>Insulin-like growth factors (IGF)</td>
<td>Contradictory data, association in Spanish population</td>
<td>Ehrmann et al. (2002b); Gonzalez et al. (2002, 2003), Haddad et al. (2002)</td>
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<td>Calpain-10</td>
<td>Polymorphisms, no association</td>
<td>Kahsari-Miller et al. (1999)</td>
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<td><strong>Genes involved in gonadotrophin action and regulation</strong></td>
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<td>Paraoxonase (PON1)</td>
<td>Polymorphism, no association</td>
<td>Leviev et al. (2001), San Millan et al. (2004)</td>
<td></td>
</tr>
<tr>
<td>Genes encoding other molecules related to insulin resistance</td>
<td>No association or linkage</td>
<td>Rajkhowa et al. (1996), Oksanen et al. (2000), Urbanek et al. (2003), San Millan et al. (2004)</td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 (PAI-1)</td>
<td>Association of 4G5G polymorphism in Greek population of PCOS women</td>
<td>Diamanti-Kandarakis et al. (2004b)</td>
<td></td>
</tr>
<tr>
<td>Tumour Necrosis Factor-α (TNFα)</td>
<td>No association</td>
<td>Hotamisligil et al. (1996, 1999), Milner et al. (1999), Escobar-Moreale et al. (2001)</td>
<td></td>
</tr>
<tr>
<td>Type 2 TNF Receptor gene</td>
<td>No association</td>
<td>Fernandez-Real et al. (1998), Peralet al. (2002)</td>
<td></td>
</tr>
<tr>
<td>Interleukin-6 gene (IL-6)</td>
<td>No linkage, or association</td>
<td>Villuendas et al. (2002), Escobar-Moreale et al. (2003a)</td>
<td></td>
</tr>
<tr>
<td>IL-6 signal transducer gp130 (IL-6ST)</td>
<td>No association</td>
<td>Escobar-Moreale et al. (2003b)</td>
<td></td>
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</tbody>
</table>

INSR, insulin receptor; VNTR, variable number tandem repeats.
gene appeared to segregate with affected status. However, there was no evidence of linkage in the remaining 18 families and overall in the 23 families the nonparametric LOD score did not reach significant levels. Furthermore, no mutations were found in the relevant coding region of the LH receptor gene in the five affected families.

These negative data are in agreement with those from Urbanek et al., 1999, where a total of 37 potential candidate genes were examined in 150 families.

*CYP11A, coding for P450 cholesterol site chain cleavage.* Investigation of CYP11A gene, which encodes the cholesterol side chain cleavage enzyme, P450scc showed a weak linkage between the CYP11A gene and hyperandrogenism in PCOS women (Gharani et al., 1996). An association study of 97 women with PCOS demonstrated also a strong association between the CYP11A 5’ untranslated region (UTR) pentanucleotide repeat polymorphism with total serum T levels. However, other studies have failed to find a significant association between CYP11A and PCOS. (Urbanek et al., 1999; Kahsar-Miller et al., 2000).

Although perturbations in the CYP11A gene cannot easily account for altered expression of other steroidogenic enzymes, the locus remains a potential candidate gene.

*CYP17, coding for 17-α hydroxylase, 17,20 lyase.* Although initial studies suggested an association between cytochrome CYP17, which encodes 17-hydroxylase/17,20-lyase, and PCOS, subsequent studies have failed to show any association or linkage of this gene to PCOS (Carey et al., 1994; Witchel et al., 1998; Diamanti-Kandarakis et al., 1999b).

However, PCOS patients show an exaggerated serum 17-α hydroxylase response to GnRH agonists. It has recently been shown that serine phosphorylation is also involved in the posttranslational regulation of 17,20-lyase activity and therefore androgen secretion. The serine residues that are phosphorylated and the kinase that mediates the phosphorylation remain to be identified.

*CYP21.* Cytochrome P450 21-hydroxylase (CYP21) encodes 21-hydroxylase, the enzyme responsible for most cases of congenital adrenal hyperplasia (CAH). Recent studies have found a significant prevalence of CYP21 mutations in PCOS women with a normal 17-hydroxypregosterone response to adrenocorticotropic hormone (ACTH) stimulation, questioning the diagnostic distinction between PCOS and CAH (Escobar-Morreale et al., 1999; Witchel and Aston, 2000).

*Androgen receptor.* Urbanek et al. (1999) studied 150 families and failed to find evidence for association of the trinucleotide repeat polymorphism in the X-linked androgen receptor gene and PCOS. However, this short CAG repeat length has been shown to be inversely associated with androgen levels (Mifsud et al., 2000).

*Sex hormone binding globulin.* Hogeveen et al. (2002) identified a polymorphism in the coding region of sex hormone binding globulin (SHBG) that encodes a missense mutation, P156L, in 4 of 482 women with PCOS, hirsutism or ovarian dysfunction.

A recent study by Xita et al. (2003) reports evidence of genetic contribution to the decreased SHBG levels frequently seen in PCOS women. They investigated the possible association of the functional (TAAAT)n polymorphism in the promoter of the gene with PCOS and lower SHBG levels. It was confirmed that women with PCOS had higher frequency of longer variable number of tandem repeats (VNTR) (more than eight repeats, range 6–11) whereas control women had higher frequency of the shorter version (less than eight). Also they report that carriers of the longer allele had lower SHBG levels within the PCOS group.

*Other steroidogenic genes.* Association and linkage studies have been performed by two groups regarding variation at the CYP19 locus (coding for P450 aromatase) and significance in the aetiology of PCOS with no significant evidence. Furthermore, Urbanek et al. (1999) examined a series of other genes in the pathways involved in ovarian steroidogenesis but none was identified as being a major factor in the aetiology of PCOS.

*Candidate genes implicated in insulin signal transduction*

Most women with PCOS both obese and lean in comparison with normal women have a degree of insulin resistance and compensatory hyperinsulinemia (Dunaif et al., 1989). Genes involved in the secretion and action of insulin may play a role and are under investigation.

*The insulin gene variable number tandem repeat.* VNTR polymorphism in the promoter region of the insulin gene (INS) regulates its expression (Bennett et al., 1995). In Caucasians, the repeats of the insulin gene VNTR are distributed in a bimodal feature, class I alleles having an average of 40 repeats and class III alleles an average of 157 repeats, with class II alleles been rare.

Waterworth et al. (1997) found strong linkage and association between the class III allele at the insulin gene VNTR (variable number tandem repeats) in the 5’ region of the insulin gene and PCOS. This allele was preferentially transmitted from heterozygous fathers but not from mothers to affected individuals.

However, in a larger study, Urbanek et al. (1999) found no evidence for linkage of the insulin gene and PCOS and no association between the class III allele of the insulin VNTR and hyperandrogenemia. In this study, the NIHCD criteria were used to choose the population as opposed to the ultrasonographic findings used by the previous one. Other studies (Calvo et al., 2002; Vankova et al., 2002) failed to show any association between the INS VNTR alleles and hyperandrogenism or PCOS. The different criteria, ethnic and geographical backgrounds might explain the conflicting results.

*The insulin receptor gene.* The impaired sensitivity to insulin action both in vivo and in vitro led to the hypothesis that genetic lesion of the insulin receptor gene or the postreceptor signalling may contribute to the pathogenesis of PCOS. Molecular studies of the coding region of the insulin receptor gene in women with PCOS have shown a large number of silent polymorphisms. The majority of those polymorphisms has also been identified in normal subjects and is considered to be common polymorphisms, which do not lead to remarkable disturbance of the function of the insulin receptor.

Recently, Siegel et al. (2002) observed a C/T single nucleotide polymorphism (SNP) in the tyrosine kinase domain of INSR, which was associated with PCOS. This SNP could be susceptibility variant for PCOS, or be in linkage disequilibrium with another INSR polymorphism, but the association is pending confirmation by others.

A number of studies have examined the insulin receptor gene sequence for major mutations since an increased insulin-dependent serine phosphorylation of the insulin receptor causing abnormalities in postreceptor activation of the pathway and therefore reducing responsiveness has been described (Dunaif et al., 1995; Moran et al., 2001). This suggests that if perturbed insulin action is integral to...
PCOS, the mechanism likely involves a target downstream of the insulin receptor. Since elegant studies by Dunai et al. (1995) have shown that in approximately 50% of women with PCOS increased insulin receptor serine phosphorylation in skeletal muscle cells and fibroblasts is associated with insulin resistance, the area of insulin receptor gene has been a major target for research, unfortunately with no concluding results.

Intriguing data come from three separate studies focusing in the area of insulin receptor gene at chromosome 19p13.3. First the National Cooperative Program in Infertility Research conducted linkage and association between a marker, D19S884 located near the insulin receptor gene and PCOS in a cohort of Caucasian families (Tucci et al., 2001). Following this, the Heritage Family Study showed evidence for statistically significant linkage between a region at chromosome 19p13.3 and androgen levels in Caucasians, providing further evidence for an important role of the region at chromosome 19p13.3 in PCOS (Ukkola et al., 2002). Thirdly, a study by Urbanek et al. 2005 (submitted for publication) provides strong, reproducible evidence for a PCOS susceptibility locus mapping to chromosome 19p13.2, at or near the dinucleotide repeat marker D19S884. The genes that code for three proteins known to map to within 100 kb of D19S884 are ELAVL1, a ubiquitously expressed mRNA-binding protein, CCL25, a thymus-expressed chemokine, and FBN3, the third member of the fibrillin family of extracellular matrix proteins. Although none of these genes is an obvious candidate for PCOS, their function needs further investigation.

Despite all the strong efforts and the impression that we are getting closer in locating the region of a putative PCOS gene, the definite answers are still escaping.

**Insulin receptor substrate proteins.** As insulin signal travels downstream intracellularly towards the second main step of insulin receptor substrate proteins, a major gene defect responsible for impaired insulin action has not been so far detected.

Several polymorphisms in IRS1 and IRS2 have been implicated in PCOS, and there is evidence of a gene dosage effect of the Gly972Arg IRS1 variant on fasting insulin and homeostasis model assessment (HOMA) values among PCOS women. A study of Ehrmann et al. (2002a) failed to provide any support on the IRS1 variable case whereas the IRS2 polymorphism was associated with the opposite results than the previous study. Finally, the Gly972Arg variant of the IRS1 gene has also been associated with lower SHBG levels in adolescent girls with a history of precocious pubarche (Ibanez et al., 2002).

**Insulin-like growth factors.** Although no evidence of a linkage with any of the insulin-like growth factor (IGF) genes was found initially (Urbanek et al., 1999), San Millan et al. (2004) tested the possibility of association of genomic variants in these genes in a series of PCOS patients and controls of Spain. A statistically significant association between homozygosity for G alleles of the Apal variant in IGF2 and PCOS was found. These alleles of the Apal polymorphism in IGF2 increase IGF2 mRNA in leukocytes and possibly result in increased liver IGF2 expression and secretion. IGF2 stimulates adrenal and ovarian androgen secretion and, together with IGF1 and IGF-binding proteins, may play a role in the pathogenesis of PCOS (Conover et al., 1992; Buyalos et al., 1995; Cataldo et al., 1998). The association between the Apal variant in IGF2 and PCOS needs to be confirmed by future studies.

**Calpain-10.** Calpain-10 is a cysteine protease that plays a role in insulin secretion and action and has been associated with susceptibility to type 2 diabetes. In a recent study, the 112/121 haplotype was associated with higher insulin levels in African-American women and an increase risk of PCOS in both African-American and white women (Ehrmann et al., 2002b).

Gonzalez et al. (2002, 2003) showed an association of the CAPN10 UCSNP-44 allele with PCOS in a Spanish population. Haddad et al. (2002), however, found no association between CAPN10 gene variation and PCOS.

**Genes involved in gonadotrophin action and regulation.**

Abnormalities in gonadotrophin secretion, particularly LH, are characteristic of PCOS. Because LH plays a permissive role in driving theca androgen production, there has been interest in exploring genes related to the regulation of LH secretion and action. Although dopamine receptor genes as well as the follistatin gene seemed originally promising fields of research regarding gonadotrophin action and regulation, the actual studies did not yield positive results.

**Dopamine receptor genes.** Dopamine inhibits GnRH and prolactin secretion. Polymorphisms have been identified in the dopamine D2 and D3 receptor genes. Homozygosity for the rare allele (allele 2) of the D3 receptor has been associated with PCOS and clomiphene resistance in Hispanic women. However, a subsequent case-control study carried out in non-Hispanic white women failed to show a significant association with allele of the dopamine D3 receptor and PCOS (Kahsar-Miller et al., 1999).

**The follistatin gene.** Follistatin is an activin-binding protein that neutralizes its biological activity both in vitro and in vivo. An increase in level or functional activity is therefore expected to arrest follicular development, increase ovarian androgen production and reduce levels of circulating FSH. These changes are all characteristic features of PCOS. An initial study of 39 affected sibling pairs demonstrated statistically significant linkage to follistatin locus on chromosome 5, and 72% of sisters were concordant for this genotype. In their affected sibling-pair analysis, it was found the strongest evidence for linkage with PCOS of any of the 37 candidate genes they studied (Urbanek et al., 1999). However, subsequent larger studies with more families conducted by the same authors and more detailed sequence analysis of the follistatin gene have not revealed significant linkage (Urbanek et al., 2000).

**Candidate genes involved in obesity and insulin resistance.** The common occurrence of insulin resistance and pancreatic α-cell dysfunction in association with PCOS and the increased risk for development of type II diabetes is now well recognised. Moreover, insulin acting through its own receptor and at high concentrations through the insulin-like growth factor I receptor stimulates steroid genesis. This has led investigators to focus on insulin resistance as a potential central abnormality in PCOS and considering the proteins promoting it as candidates for PCOS genes.

**Peroxisome proliferator-activated receptor-γ gene.** Activation of peroxisome proliferator-activated receptor (PPAR)γ promotes differentiation of adipocytes, increasing insulin sensitivity. The PPARγ gene (PPARG) contains a common SNP, Pro12 Ala. It has been shown that Ala 12 alleles of PPARG favour weight gain in obese adults and in obese hyperandrogenic girls and adolescents. They also preserve insulin sensitivity in Caucasian men and women presenting with PCOS (Hara et al., 2002). Recently, a
marginally significant decrease in the frequency of the Ala12 allele in Finnish PCOS patients has been reported. However, this polymorphism has shown no association either with PCOS or insulin resistance in hyperandrogenic adolescents from the USA (Witchel et al., 2001) or in women from Spain (San Millan et al., 2004).

**Human sorbin and SH3 domain-containing 1 gene.** Human sorbin and the SH3 domain-containing 1 (SORBS1) protein is involved in insulin-mediated glucose uptake. The Thr228Ala variant in its gene (SORBS1) may play a role in the genetic predisposition to obesity and type 2 diabetes. The SORBS1 Ala228 allele was found to play a protective role against the development of these disorders in Chinese subjects (Lin et al., 2001), however, conflicting results have been reported in a large European study (Nieters et al., 2002). Moreover, no association with this allele with either adolescent hyperandrogenism or PCOS has been found (Witchel et al., 2003).

**Paraoxonase.** Paraoxonase-1 (PON1) is a serum high-density lipoprotein (HDL)-associated enzyme with antioxidant properties. A polymorphism in PON1 (-108T/C) is more frequent in nondiabetic subjects showing abnormal fasting glucose concentrations (therefore, suspected to have insulin resistance) compared with subjects with normal serum glucose concentrations (Levie et al., 2001). Since the -108T alleles may reduce paraoxonase expression and secretions, increasing oxidative stress, it is possible that homozygosity for –108T alleles, and PCOS might lead to a higher oxidative stress in these women, contributing to insulin resistance (San Millan et al., 2004).

**Genes encoding other molecules related to insulin resistance.** Among the other genes tested, no association has been reported between PCOS and genomic variants in the genes encoding glycoprotein, protein tyrosine phosphatase 1B, and adipsin (San Millan et al., 2004).

**Candidate genes of indices in chronic inflammation.** Abnormalities in endothelial function and elevated cardiovascular risk factors have also been observed in PCOS women making the associated proteins possible candidate genes for PCOS. Additionally, the secretory products of adipose tissue including tumor necrosis factor TNF-α and IL-6 which promote insulin resistance and hyperandrogenism have been implicated in PCOS pathophysiology.

**Plasminogen activator inhibitor-1.** Elevated plasminogen activator inhibitor-1 (PAI-1) levels have been associated with increased cardiovascular risk and increased thrombogenic tendency. Recently a 4G5G polymorphism in the promoter region of PAI-1 gene has been associated with increased plasma PAI-1 levels in Greek women with PCOS compared with controls (Diamanti-Kandarakis et al., 2004b).

**TNF-α gene.** Tumor necrosis factor (TNF)-α is a cytokine secreted by adipose tissue that plays a key role in mediating insulin resistance (Hotamisligil et al., 1996; Hotamisligil, 1999). Serine phosphorylation of IRS1 appears to be the mechanism for TNFα-mediated insulin resistance. Serum TNFα levels are elevated in patients with hyperandrogenism and PCOS but studies have shown no association between polymorphism in its gene (TNF) and hyperandrogenism or PCOS (Milner et al., 1999; Escobar-Morreale et al., 2001). However, when considering hyperandrogenic patients and healthy controls as a whole, carriers of TNF-308A alleles presented with increased basal and luteolide-stimulated serum androgens and 17-hydroxyprogesterone levels, suggesting that this variant contributes to hyperandrogenism (Escobar-Morreale et al., 2001).

**Type 2 TNF receptor gene.** The type 2 TNF receptor (TNFR2) mediates most of the metabolic effects of TNFα. Serum levels of TNFR2 are increased in obese individuals, correlating with indexes of insulin resistance (Fernandez-Real et al., 1998; Peral et al., 2002). In an initial study of 103 hyperandrogenic patients (42 with PCOS) and 36 controls from Spain, it was observed that the Arg196 allele of the Met196Arg variant in exon 6 of the TNFR2 gene tended to be more frequent in hyperandrogenic patients than in controls (Peral et al., 2002), suggesting a possible role of the TNFα system in the pathogenesis of hyperandrogenic disorders.

**Interleukin-6 gene.** Interleukin-6 (IL-6) is secreted from the adipose tissue. It promotes liver secretion of C-reactive protein, which was both found increased in obese women, and in PCOS (Escobar-Morreale et al., 2003a). It was recently found that common G alleles of the −597A and −74G/C IL-6 gene polymorphisms which are in linkage disequilibrium are associated with hyperandrogenism in a study involving 85 patients and 25 healthy women from Spain (Villuendas et al., 2002). Moreover, when studying controls alone, carriers of G alleles presented higher serum IL-6, 17-hydroxyprogesterone and 11-deoxycorticisol levels compared with subjects homozygous for the uncommon −597A or −174C alleles, suggesting a protective role for the uncommon alleles against adrenal hyperactivity and hyperandrogenism.

**IL-6 signal transducer gp 130 (IL-6ST).** IL-6 actions are mediated by a heterodimeric receptor consisting of two membrane-bound glycoproteins: an 80 kDa IL-6 binding unit (IL-6Ra) and a 130 kDa IL-6 signal transducer (gp130). It was recently found that the uncommon Arg148 allele of the Gly148Arg polymorphism in the gp130 gene (IL-6ST) was more frequent in controls compared with hyperandrogenic patients. Controls carrying Arg148 alleles had lower 11-deoxycorticisol and 17-hydroxyprogesterone concentrations; a lower response of androstenedione to 1–24 adrenocorticotropin and an almost significant decrease in free T levels (Escobar-Morreale et al., 2003b). As occurred with the IL-6 variants, the wild type allele was associated with hyperandrogenism, whereas the uncommon Arg148 allele in gp130 had a protective effect against androgen excess and adrenal hyperactivity. Therefore, the influence of proinflammatory genotypes on hyperandrogenism and PCOS might result from the interaction between predisposing and protective variants in several different genes.

**Conclusion**

Steadily the numbers of candidate genes are increasing but they have not yet led us all the way out of the labyrinth. Collectively, these findings add important information to the PCOS genetic background, raising the possibility of multiple genetic components being involved. However, the current genetic studies have failed to identify specific gene or genes, with clear clinical significance and, practically, do not take our clinical approach any further from the significant initial observation that the positive family history is common in women with PCOS. Although additional larger case-control studies are clearly required to produce clinically meaningful results, it can be concluded that genetic abnormalities in androgen steroidogenesis and

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in insulin action have been detected in PCOS patients, but combinations of different genes polymorphisms may be required in order to explain the heterogeneity of the syndrome.

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gene are associated with hyperandrogenism. J Clin Endocrinol Metab 87,1134–1141.


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