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Review article

Genetics of polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a genetically based disorder which reflects multiple potential aetiologies and variable clinical presentations. It is clearly a heterogeneous syndrome, and current proposed diagnostic criteria include a number of disorders with similar phenotypes but radically different aetiologies. The lack of well-defined diagnostic criteria makes identification of PCOS confusing to many clinicians and seriously delayed the clarification of its genetics, aetiology, clinical associations and assessment of treatment. There is no universally accepted clinical definition for PCOS. In this review the genetic causes and diagnosis criteria of PCOS will be discussed.

Key words: PCOS, Heterogeneous syndrome, Genetics .

Introduction

Different family studies have been proposed that polycystic ovary syndrome (PCOS) has a genetic basis because a high number of female relatives of PCOS patients are affected. These studies have suggested that because of familial aggregation of hyperandrogenemia in first degree relatives of PCOS patients, it is a genetic trait (1, 2). PCOS affects 4% to 12% of women of reproductive age (3-5). Despite its frequency, the PCOS is still a difficult diagnosis in endocrinology, gynaecology and reproductive medicine. Since first description of PCOS by Stein and Leventhal in 1935 (6), the aetiology of this syndrome is still speculative while its pathophysiology appears to be both multifactorial and polygenic. There is considerable heterogeneity of symptoms and signs amongst women with PCOS, and for an individual, these may change over time (7,8). In fact, considering PCOS as one of persistent anovulation with a variety of aetiologies and clinical manifestations is far more useful. PCOS should be defined by exclusion of related disorders, such as Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, androgen-producing tumours and nonclassical adrenal hyperplasia (9,10). Further identification of specific causes, and exclusion of the multiple phenocopies that make up PCOS, will assist its diagnosis (11).

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Genetic of PCOS

Previous studies suggest that genetic factors play a major role in the etiology of PCOS (1,12). However, the mode of inheritance of PCOS remains unknown, and recent studies indicate that this disorder could be a complex trait (13). This means that several genes are interacting with environmental factors to provoke the phenotype (14). In contrast, biochemical parameters, including fasting insulin levels or hyperandrogenemia, seem to be highly heritable parameters, suggesting that some clinical signs, symptoms, or biochemical parameters of PCOS could be transmitted as mendelian autosomal dominant (15) or X-linked traits (16), but the genetic studies have not as yet concluded the pattern of heredity (17). While studies, so far, are unable to exclude an autosomal or X-linked dominant mode of inheritance, the heritability of PCOS is probably more complex, similar to that of type 2 diabetes mellitus or cardiovascular disease. However, a positive family history appears to be the most informative risk factor for the development of PCOS. Furthermore, environmental factors alter the clinical and biochemical presentation in those with genetic predisposition to PCOS.

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There are apparent problems which make genetic studies of PCOS difficult to perform. The heterogeneity and lack of universally acceptable clinical or biochemical diagnostic criteria have been discussed. PCOS is a disorder which primarily affects women of reproductive age and it is therefore difficult to study in more than one generation. There is no commonly accepted male phenotype. Male pattern premature balding has been demonstrated in male relatives in familial PCOS studies (16).

Chromosomal abnormalities

A relation between PCOS with the X chromosome aneuploidies and polyploidies in addition to other cytogenetic abnormalities has been confirmed. Some of the cases of PCOS may represent an intermediate condition in a spectrum that extends from the streak gonad of Turners syndrome to the normal ovary. The concept is that at least some cases of PCOS may be due to X chromosomal factors causing an abnormal follicular apparatus (18). In addition, large deletion of the long arm of chromosome 11 was seen in some of the PCOS cases (19). However, there is no large cytogenetic study to identify karyotype abnormalities.

Molecular abnormalities

There are different candidate genes as a cause of PCOS; such as genes involved in steroid hormone synthesis and action, genes involved in carbohydrate metabolism and fuel homeostasis, genes involved in gonadotropin action and regulation; and genes in the major histocompatability region, which could account for certain PCOS features. Increased androgen secretion and insulin resistance persist in cultured theca cells and skin fibroblasts, respectively, from women with PCOS, which suggest that these are intrinsic, presumably genetic, defects.

Different studies have indicated a genetic susceptibility to PCOS. It was shown that polycystic ovaries and hyperandrogenemia are present in 50% of sisters of affected women. Therefore genetic analyse of candidate genes have been performed. Both linkage and association studies have suggested that PCOS can be explained by the interaction of a small number of key genes with environmental, particularly nutritional factors. Hyperandrogenaemia is genetically determined and the result of familial studies indicating that hyperandrogenism clusters as a dominant genetic trait (20). The steroid synthesis gene CYP11a, coding for P450 cholesterol side chain cleavage and the insulin gene regulatory region may be involved. However, it is unlikely that the hyperandrogenaemia of PCOS is principally determined by polymorphisms or mutations in the genes encoding a single steroidogenic enzyme activity, such as CYP17 or CYP11a (21-24). In addition, an increase of mRNA abundance in PCOS has been found in corresponding to the genes of aldehyde dehydrogenase-6 and retinol dehydrogenase-2, which both increases the expression of 17a-hydroxylase (25). Recent studies have found a significant prevalence of CYP21 mutation, gene encode the 21-hydroxylase enzyme mimic the PCOS phenotype, in the supposed PCOS population (26). Mutations in the insulin receptor gene cause severe insulin resistance (the type A syndrome) associated with PCOS. A linkage analysis study found association between a marker (D19S884 at 19p13.3) that is located 2 megabases centromeric from the insulin receptor gene and PCOS. This locus emerges as a strong candidate region deserving of detailed investigation for the identification of the putative PCOS gene (27). Finally abnormalities in gonadotropin secretion, particularly LH, are characteristic of PCOS, which promote exploring genes related to the regulation of LH secretion, LH bioactivity, and LH action.

Clinical discussion

PCOS includes a variety of potential signs and symptoms, including oligo-ovulation, biochemical or clinical hyperandrogenism, polycystic ovaries, and hyperinsulinemia, but no single diagnostic criterion is recommended for diagnosis of PCOS. In addition, PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events. Insulin resistance and elevated serum LH levels are also common features in PCOS (10, 28, 29). Among different criteria, hyperandrogenemia, specifically elevated bioavailable testosterone, and the recognition of oligo-ovulation are academically appealing. Many support a combination of hyperandrogenemia and oligo-ovulation, in the absence of known causes, as diagnostic criteria. While, many others are using ovarian morphology to identify and diagnose the syndrome (9). To help solving this issue, the Rotterdam consensus conference proposed to include the ultrasonographic (U/S) follicle count as a new diagnostic criterion, in addition to hyperandrogenism and oligo-anovulation (30). Unfortunately this assessment does not offer enough trustworthiness worldwide (31). Some publications confirm the unreliability of the U/S images by the help of magnetic resonance images (MRI) (32).

Overall, the three recommended criteria are: 1/ oligoamenorrhoea, 2/ any form of hyperandrogenemia, either clinical (hirsutism and acne), or endocrine (the hormonal diagnosis of high androgen levels), and 3/ the ultrasound picture of

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polycystic ovaries. These three are the major criteria but in order to make the diagnosis it needs to fulfil only two out of three. This makes PCOS a heterogeneous disease (30). Normal ovulatory women with PCO (referring only to the ovarian morphology) are not considered having PCOS. A subgroup of these women may, however, have subtle abnormalities resembling PCOS.

Oligomenorrhea

Oligomenorrhea or dysfunctional bleeding are frequently early and dominant symptoms of the anovulatory component of PCOS. The menstrual irregularity of the PCOS is chronic and can be manifested in several different ways. Probably the most common is irregular menstruation due to anovulation. Some women with PCOS have long-lasting amenorrhea associated with endometrial atrophy. Some women have regular cycles at first and experience menstrual irregularity in association with weight gain. While, sometimes the onset of PCOS is peripubertal. In fact, there is strong evidence of a peripubertal onset of the PCOS and it has been used as a diagnostic criterion (33).

Infertility

Infertility was included in the original description of PCOS by Stein and Leventhal (6). The prevalence of infertility, caused mainly by anovulation, in PCOS women varies between 35% and 94% (34). According to one retrospective study, however, women with PCOS are as likely to have children as healthy women, although often after infertility treatment (35). Some studies have also described an increased miscarriage rate in PCOS, the mechanism of which is inadequately understood. It has been suggested that high follicular phase concentrations of LH have a harmful effect on rates of conception and miscarriage (36,37).

Hyperandrogenism

Hyperandrogenism is the second essential characteristic of PCOS and is the most consistent biochemical finding in all women with PCOS (38). Familial aggregation of reproductive endocrine biochemical abnormalities in PCOS relatives suggests that these traits have a genetic basis (1). Clinically, the most common sign of hyperandrogenism in PCOS women is hirsutism. The range of the prevalence of hirsutism in PCOS women varies between 17% and 83%. Another common sign of hyperandrogenism is acne. Thus, an adolescent female with moderate to severe acne should be investigated for PCOS. Furthermore, the progress or persistence of acne into adulthood is unusual and should raise awareness. However, it has also been shown that hyperandrogenism may be related to overt signs of virilization, i.e. male pattern balding, alopecia, increased muscle mass, a deepening voice or clitoromegaly but these signs partly resolves before menopause in women with PCOS. These women tend to gain more regular menstrual cycles with increasing age (40 years and more) (8).

Gonadotrophin secretion

An inappropriate gonadotrophin secretion is associated with the classic form of PCOS. Compared with the follicular phase of the normal menstrual cycle, women with PCOS exhibit an unreasonably high LH secretion with comparatively constant low FSH secretion. Therefore, an elevated LH/FSH-ratio of 2-3/1 is commonly used to indicate abnormal gonadotrophin secretion. The prevalence of increased serum LH in PCOS ranges from 30% to 90 % (38,39).

Anti-mullerian hormone

Anti-Mullerian Hormone (AMH) measurement in the serum could be a replacement for antral follicle count in the diagnostic criteria of PCOS. In circumstances where accurate U/S data are not available, AMH could thus be used instead of the follicle count as a diagnostic criterion (22).

Obesity

Although there are no controlled systematic studies to determine the exact prevalence of obesity, most investigators have found that 30-50% of PCOS women are obese with a tendency to have an increased waist-hip ratio, or abdominal obesity. Certainly, many metabolic derangements improve with weight loss, but PCOS is not cured by weight reduction. Almost always, individuals with PCOS gain weight very easily and lose it only with great effort. They have significantly increased glucose and plasma insulin levels during an oral glucose tolerance test compared with obese control women (25). In facts, PCOS increasingly has been linked to abnormalities of insulin and glucose metabolism.

Insulin resistance

Recent insights into the pathophysiology of PCOS have shown insulin resistance to play a considerable role (40). Upper-body obesity is a key component of the insulin resistance (IR) syndrome (41). Acanthosis

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nigricans is a grey-brown velvety discoloration of the skin caused by hyperkeratosis and papillomatosis usually in the areas of neck, axillae, groin and under the breast. This condition is often associated with glucose intolerance and hyperandrogenism (42).

Conclusion

The importance of genetic and environmental factors in the etiology of PCOS is unclear. Current concentration has focussed on importance of the genetics factors, because molecular genetic approaches can now be employed to assess the contributions of individual genes in complex genetic disorders. Both autosomal and X-linked dominant modes of inheritance have been recommended to describe the observed familial clustering of cases of PCOS. Lack of a sensitive diagnostic marker has previously made it difficult to follow segregation of the syndrome in families. Ovarian ultrasound enables definition of the phenotype more accurately than can be realizing by consideration of symptoms or biochemical parameters of the syndrome alone, and can thus be used to more accurately assign affected status.

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