Polycystic Ovary Syndrome: The Genetic Aspect

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Introduction

Polycystic ovarian syndrome (PCOS) is a spectrum of diseases comprising the polycystic-like ovary (PCO) together with the symptoms of excess androgen production such as hirsutism, oily skin and acne as well as the manifestations of oligo-ovulation, for instance, oligomenorrhea, secondary amenorrhea, or abnormal uterine bleeding. Patients acquiring this syndrome may also experience difficulty in getting pregnant. The infertility problem in PCOS cases is thought to be due to several causes such as ovulatory disorder and the excess in androgen production resulting in poor quality of follicles and subsequently poor fertilization or low implantation rates. It is noticed for years that PCOS tend to occur in the persons with family history of oligomenorrhea or infertility, and thus the genetic inheritance of PCOS is a reasonable hypothesis. Based on the study of first-degree relatives of women diagnosed with PCOS, it was thought that polycystic ovarian syndrome has some degree of genetic predisposition. None of these early family studies, however, convincingly established mode of inheritance because too few families were studied, parental phenotypes were not established, and the male phenotype was uncertain. Despite the lack of comprehensive phenotype information, the older literature clearly suggested clustering of PCOS in families, and suggested a mode of inheritance most consistent with an autosomal dominant pattern. During the past decade, more information regarding the pattern of inheritance of polycystic ovarian syndrome was revealed and thus it is becoming clearer for us to understand the complexity of inheritable route of this syndrome. This article reviews the up-to-date information regarding our current understanding of the genetic component of this syndrome.

Genetic aspect of PCOS: Familial studies

During the 1990s, genetic origin of PCOS attracted the interest of several groups of scientists around the world. Family studies of PCOS were thus re-investigated with more careful phenotyping. Although small numbers of families were investigated the findings were suggestive of an autosomal dominant or modified dominant mode of trait inheritance. The study by Legro and colleagues was the largest of these, encompassing a prospective analysis of 80 PCOS women and 115 of their sisters. In this study, 22% of the sisters of the affected women fulfilled the diagnostic criteria for PCOS and an additional 24% were hyperandrogenemic but had more than six menses per year. This led to the conclusions that there is familial clustering of hyperandrogenemia with or without oligomenorrhea, and that hyperandrogenemia is inherited as a dominant trait.

The fact that there is concordance of phenotypes in identical twin pairs provides strong evidence for a genetic component of PCOS. Several case reports describe PCOS in monozygotic twins, leading the authors to conclude that a PCOS ovarian morphology is not shared by monozygotic
twins and that PCOS is not caused by a single autosomal gene. However, it is important to note that the authors did report a significant genetic influence on levels of androstenedione glucuronide in these twin pairs.

In vitro studies of molecular and biochemical phenotype in PCOS cases

It is reasonable to presume that if PCOS is a genetic disease, cells from PCOS women would show a stable biochemical or molecular phenotype that distinguishes them from normal cells. Studies conducted on thecal cells collected from follicles from PCOS and normal ovaries revealed that PCOS thecal cells retained biochemical and molecular features of increased production of progestosterone, 17α-hydroxyprogesterone and testosterone; increased expression of CYP11a, CYP17 (CYP stands for Cytochrome P450) and type II 3β-hydroxysteroid dehydrogenase, but not steroidogenic acute regulatory protein (StAR) mRNA, and increased transcription of the CYP17, but not the StARGene. These alterations parallel findings made on freshly isolated thecal cells studied in short-term culture, measurements of mRNAs encoding steroidogenic proteins in freshly isolated theca and ovarian responses to human chronic gonadotropin (hCG) stimulation in vitro. Dunaif and colleagues also identified differential patterns of phosphorylation of the β-subunit of the insulin receptor in ovarian cancer cells and fibroblasts from women with PCOS. Approximately 50% of the sample population of PCOS women studies showed the increased insulin receptor serine phosphorylation. This observation was recently confirmed in ovarian tissue.

Collectively, the family studies and the experiments conducted on cells in culture are consistent with the concept that genetic factors contribute to PCOS. However, the number of genes involved is not known, although the preponderance of data suggests a dominant or modified dominant pattern of inheritance indicative of an oligogenic disease.

Molecular alterations in other cell types besides reproductive organs

It is clear that, although its reproductive features characterize PCOS, multiple organs are affected. Excessive thecal cell androgen secretion is characteristic of PCOS. Alterations in the profile of luteinizing hormone (LH) secretion (pulse frequency and amplitude) and excessive adrenal androgen production are also common in women with PCOS. Insulin resistance can be demonstrated in 50% or more of PCOS women, the primary issues affected being skeletal muscle and adipose tissue. Pancreatic β-cell dysfunction, independent of obesity, is also associated with PCOS. The insulin resistance and β-cell dysfunction are undoubtedly linked to the increased risk of type II diabetes mellitus in PCOS. Higher rates of early pregnancy loss have been documented in PCOS. Moreover, there is increased risk of endometrial adenocarcinoma. The early pregnancy wastage has been attributed to an abnormal steroid milieu resulting from hypersecretion of LH. The increased incidence of endometrial adenocarcinoma is usually attributed to the unopposed action of estrogen on the endometrium. However, an alternative explanation, yet to be explored, is that an intrinsic abnormality in endometrial cell function causes early pregnancy loss and neoplasia. One commonly asked question is that whether there is any evidence for common metabolic/molecular abnormalities among different cell types in PCOS. The preliminary studies by Wood and colleagues demonstrated altered expression of the secreted frizzled-related protein 4 in cultured thecal cells, cultured dermal fibroblasts, freshly isolated adipocytes and skeletal muscle biopsies, as well as cultured skeletal muscle myocytes from women with PCOS. This suggests that expression of a single gene can be dysregulated in multiple cell types. Whether the multiple endocrine abnormalities are directly linked, or are independent features reflecting the contribution of diverse genetic and environmental factors, have considerable significance for studies on the genetics of PCOS. Hypotheses built upon tight association of these disturbances are most compatible with the notion that PCOS is caused by a limited number of genetic/environmental factors. The alternative relates the possibility of a polygenic/multifactorial disorder that would require comprehensive phenotyping of subjects to facilitate identification of causative molecular and environmental factors in specific disease subsets, as in the case of the genetics of type II diabetes.

PCOS and metabolic imprinting

Besides the genetic hypothesis, another alternative to the origin of PCOS is that PCOS is caused by environmental factors that result in a stable metabolic
imprint. The idea of permanent metabolic imprinting is attaining acceptance in the biomedical community, based largely on the examination of the consequences of intrauterine environment on subsequent adult disease. It is noteworthy that prenatal exposure of female rhesus monkey fetuses to testosterone has been reported to promote the development of PCOS-like biochemical features, including increased LH levels and impaired insulin secretion and sensitivity in adult life. The notion of a stable metabolic (non- genetic) imprint arising during development, which might influence organogenesis or cellular composition (e.g. cell hypoplasia or hyperplasia), is not difficult to envision. However, a stable metabolic (epigenetic) imprint in dividing cells is more difficult to explain, unless there are alterations in expression of imprinted genes or post-translational modifications of long-lived proteins that are passed down to daughter cells in sufficient quantities to alter cellular function. Alternatively, an extra-genomic replicating molecule would have to be contemplated. These considerations lead us to favor a primary role for genetic factors in the pathophysiology of PCOS, although environmental factors (e.g. obesity) could clearly exacerbate metabolic consequences of a variant genotype predisposing to PCOS.

PCOS: Association studies and linkage analysis

Association studies and linkage analysis for candidate genes, together with genome-wide scanning using non-parametric methods, are used to identify the genes causing diseases where several different genetic loci are likely to contribute to the phenotype. The latter approach is ideal because it makes no assumptions regarding the gene(s) involved, the mode of inheritance, disease penetrance or prevalence. Unfortunately, no investigatory team studying PCOS has been able to assemble a sufficient number of families with affected sib-pairs to perform a genome-wide scanning at the present. Consequently, the existing literature is built exclusively on association and linkage studies for selected candidate genes.

This reflects difficulty in accruing families with multiple affected sisters and available parents, despite the fact that PCOS is a common disorder. However, testing available family DNA sets for candidate genes is not an unreasonable exercise in the absence of sufficient populations to conduct a genome-wide scan. Yet, the universe of possible candidates from which to choose in the case of PCOS is potentially large and the number of wrong guesses for PCOS candidate genes is expected to be high. Wrong guesses are not necessarily without value, since the exclusion helps to narrow the field of possibilities and adjusts the level to which the gene products are emphasized in models of PCOS pathophysiology. To date, the candidate genes that have been investigated include those 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 histocompatibility region. Among the most promising candidate genes for which there is evidence for linkage or association are the CYP11A1, the insulin gene, and a locus near the insulin receptor on chromosome 19p13.3. Although mutations in the insulin receptor gene have been found in rare cases of PCOS, the allele at 19p13.3 is not likely to be the insulin receptor, as it lies 2 megabases centromeric to the insulin receptor gene. Folliculostatin, originally thought to be a viable candidate gene, appears less likely to be involved, based on recent studies which failed to identify variants in the folliculostatin gene strongly associated with PCOS. Notably, two different studies have fingerprinted the same locus at 19p13.3, raising considerable interest in this region. Chromosome 19 is gene-rich and a number of putative and known genes are in the vicinity D19S884 and deserve special scrutiny.

Other candidate genes for PCOS

There is a need to increase the number of candidate genes to test for association and linkage with PCOS. One strategy to identify candidate disease genes is to define differential patterns of transcript and protein expression in normal and diseased tissues or cells. By examining those genes whose transcripts or protein products are increased or reduced in the diseased cells, pathways and regulatory networks may emerge which point to the underlying molecular pathology. As noted earlier, PCOS cells in long-term culture have been shown to display stable biochemical and molecular differences from normal cells, allowing for relative comparison of gene and protein expression. The methodology that can be used to make these comparisons include suppression subtractive hybridization (SSH), DNA micro-array analysis and a
novel protein chip technology employing surfactant-enhanced laser desorption ionization coupled with time-of-flight mass spectrometry. DNA array analysis and SSH may potentially overlook alternative splicing of transcripts. These technologies also cannot detect gene variants that might influence protein function but not level of transcript expression, or differences in post-translational modification of proteins (e.g., proteolytic processing, phosphorylation). These are also weaknesses that can be overcome by the protein chip methodology.

Conclusion

Polycystic ovarian syndrome comprises a spectrum of manifestations including acne, oily skin, oligomenorrhea, amenorrhea, abnormal uterine bleeding and infertility. The common findings on the investigation include polycystic ovary (PCO), hyperandrogenemia and the increased LH: FSH ratio. This syndrome is among the most common endocrinopathies found in women of the reproductive age and several hypotheses have been proposed regarding the etiology of this syndrome. One of the most likely explanation for the occurrence of this syndrome is genetic alteration that can be passing from one generation to the next. The improvement in molecular biology techniques as well as the more information we obtained from the human genome project will, hopefully, lead us to understand more about the possible genetic components of PCOS. The precise understanding of the pathogenesis of this syndrome will, thus, help us to properly tackle with the consequences of this syndrome or even possibly prevent its occurrence in the future generations.

References


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