Research Progress on the Correlation between Genetic Polymorphisms and Polycystic Ovary Syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder in women, with complex and unclear pathophysiological mechanisms. It is mainly caused by the interaction between the central nervous system, the pituitary gland, the adrenal glands, the ovaries, and extra glandular tissues. In addition to dysfunction of the hypothalamus and ovaries, inflammation, excessive androgen, insulin resistance, and obesity are also relevant mechanisms. The influence of genetic factors is also significant. Currently, there is insufficient research on the genetic level of PCOS etiology. This article summarizes the relevance of genes involved in hormone regulation, metabolism, inflammatory cytokines, and other genes to PCOS from the perspective of genetic polymorphisms in the pathogenesis of PCOS. It aims to explore the possible mechanisms of genetic polymorphisms leading to PCOS and provide references for the etiological research, precision treatment, and diagnosis of PCOS.

Keywords: Polycystic Ovary Syndrome, Heredity, Polymorphism, Gene.

1. Introduction

PCOS is a reproductive, metabolic, and psychological disorder that affects 5-18% of women throughout their life cycle, with complex causes including genetic and epigenetic susceptibility, hypothalamic and ovarian dysfunction, hyperandrogen, insulin resistance, and obesity-related mechanisms[1]. In 1935, Stein and Leventhal first reported the relationship between amenorrhea and polycystic ovary[2]. According to the recommendations of the international evidence-based guidelines for the evaluation and management of PCOS in 2018, the Rotterdam diagnostic criteria are used as the international diagnostic criteria for PCOS[3]. Patients often have irregular menstruation, hirsutism, infertility, acne, acanthosis nigricans, hirsutism, hair loss and abdominal obesity, which are usually diagnosed during childbearing period. They have type 2 diabetes, hypertension, cardiovascular disease, obstructive sleep apnea, endometrial cancer, depression and anxiety, and an increased risk of nonalcoholic fatty liver disease. The risk of pregnancy complications such as abortion, gestational diabetes mellitus, pregnancy induced hypertension, high rate of cesarean section and abnormal fetal growth are all increased[4]. Dutch scholars have found that the similarity between identical twin sisters and PCOS is about twice that of fraternal twins and other sisters, which proves the serious influence of genetic factors on the pathogenesis of PCOS[5]. PCOS is a common hereditary disease with high heritability and phenotypic heterogeneity[6]. It is particularly important to explore the role of gene polymorphism in PCOS. This paper reviews the related researches in recent years.

2. Involved in Regulating Hormone-related Genes associated with PCOS

2.1 Luteinizing Hormone and Chorionic Gonadotropin

LHCR Gene

LHCR are members of the G protein coupled receptor superfamily. LHCR is activated by luteinizing hormone (luteinizing hormone, LH) and human chorionic gonadotropin (human chorionic gonadotropin, HCG). LHCR is expressed in granulosa cells, membrane cells and luteal cells, and is essential for estradion production, ovulation and luteal formation[7]. The gene is located in the short arm of chromosome 2 (2p16.3), which is a single copy gene composed of 11 exons and 10 introns. The mature form of LHCR on the cell surface is a glycoprotein composed of 675 residues with a molecular weight of 85-95kDa[8]. LHCR can participate in androgen production, and excessive androgen is one of the related pathogenesis of PCOS patients. Exon 10 of LHCR contains rs2293275 and rs12470652, which leads to changes in amino acids at position 312 and 291, respectively. A case-control study analyzing the association between LHCR variation and PCOS in Punjab in northwest India showed that there were statistically significant differences in genotype and allele frequencies between the case group and the control group. The mutation genotype (AA) and mutation allele (A) of rs2293275 were 1.7times and 1.3 times of the risk of PCOS, respectively, and the risk of mutation allele (C) of rs12470652 to the progression of PCOS was 2.3. Compared with healthy controls, the levels of cholesterol and triglyceride were higher, the levels of high density lipoprotein were lower, and the levels of total testosterone and LH were higher in PCOS patients[8]. In an European adolescent study, it was found that total testosterone levels in PCOS patients with LHCRrs2293275 minor alleles were significantly higher than those with major allele homozygotes[9]. rs13405728 may be a genetic risk factor for PCOS in Asian populations[10]. These studies can fully conclude that the gene polymorphism of LHCR is closely related to PCOS, but there are many mutations of LHCR in different races, which may be the result of single nucleotide or...
multiple nucleotides common mutation, and the conclusions of the same gene locus are contradictory, and the specific mechanism needs more data experiments to further explore. In the rat model experiment of PCOS, phosphorylated Janus kinase 2 (phosphorylated signal transducer and activator of transcription (p-JAK2/p-STAT3) participated in the regulation of ovarian folliculogenesis by overexpressing LHCGR, cytochrome P450 17α and down-regulating the expression of follicle-stimulating hormone receptor (FSHR), cytochrome P450 19 and aromatase, which led to the stagnation of antral follicular development and the morphology of polycystic ovary. Moreover, the use of exogenous Janus kinase 2 inhibitor AG490 can be improved[11]. In addition, serum miR-592 in patients with PCOS was significantly decreased and negatively correlated with serum LHCGR level. Overexpression of miR-592 in granulosa cells inhibited cell viability and the transition from G1 phase to S phase. Knocking down LHCGR inhibited cell viability and cell cycle progression. LHCGR cotransfection reversed the inhibitory effect of miR-592[12]. These studies provide a new idea for the clinical treatment of PCOS from the perspective of LHCGR.

2.2 FSHR Gene

FSHR gene is located on chromosome 2 p21-p16 and are composed of 10 exons and 9 introns[13]. FSHR gene is adjacent to LHCGR, and FSHR, as the receptor of follicle stimulating hormone (FSH), can stimulate the development of ovarian follicles[14]. Under normal circumstances, the ovaries secrete a small amount of androgens, but PCOS patients often show excessive androgens, inhibition of estrogen production, and abnormal regulation of the hypothalamic-pituitary-ovarian axis itself, thus affecting the ovum formation and ovulation process of follicular development and hormone secretion. PCOS can be characterized by decreased FSH secretion and increased LH levels. Studies have shown that the variant rs2300441 in FSHR has a significant impact on FSH levels in PCOS patients and Chinese Han female control group. Single nucleotide polymorphism (SNP) of FSHR gene is associated with ovarian reserve and ovarian function. Variant rs2300441 may be a potential marker for ovarian response and reproductive outcomes in patients undergoing assisted reproductive technology (ART)[15]. FSHR polymorphism can change the phenotype of PCOS. SNPs of FSHR gene affect the susceptibility of PCOS, and also affect the receptor's sensitivity to exogenous FSH during ovulation induction therapy. In addition, SNPs in the LHCGR receptor and SNPs in the FSH-β gene may determine a woman's susceptibility to PCOS[13]. Tanshinone IIA, the main component of salvia miltiorrhiza, can change the balance of androgens and estrogens by inhibiting the reduced expression of FSHR and aromatase, thus playing a therapeutic role in PCOS [16]. FSHR gene affects the female reproductive system in many ways, and there is a close relationship between FSHR gene and PCOS, especially in ovarian dysfunction in this disease. It is particularly meaningful to conduct more experimental studies and analysis to demonstrate FSHR gene polymorphism.

2.3 SHBG Gene

SHBG is a glycoprotein produced by the liver, a high affinity and specific binding steroid. SHBG is present in fetal circulation and umbilical cord blood, and in certain clinical observations and reports, circulating SHBG levels have been shown to be inversely correlated with markers of non-alcoholic fatty liver disease and insulin resistance. Decreased SHBG levels increase the bioavailability of androgens, leading to ovarian lesions, anovulation, and phenotypic characteristics of PCOS[17]. Most women with PCOS have metabolic abnormalities. SHBG is a transporter that binds estrogen and androgens and regulates their biological activity, and often reduced SHBG is used as an indicator of androgen hyperplasia in women with PCOS. Low serum SHBG is considered to be a biomarker of metabolic abnormalities and is associated with insulin resistance, compensatory hyperinsulinemia, and abnormal glucose and lipid metabolism in PCOS patients, as well as the long-term prognosis of PCOS. Therefore, SHBG gene polymorphism plays a crucial role in the occurrence and development of PCOS. Hepatic nuclear factor-4α (HNF-4α) is an important transcription factor in SHBG synthesis. HNF-4α binds to the cis-element DR1 in the SHBG promoter to initiate transcription and regulate liver SHBG levels by regulating glucose and lipid metabolism and inflammatory factors [18]. However, whether HNF-4α can further affect PCOS by affecting SHBG gene synthesis remains to be studied.

3. Genes Involved in Metabolism Related to PCOS

3.1 INSR Gene

INSR is a part of insulin signaling pathway. The INSR gene, which is located on the short arm of chromosome 19 and consists of 22 exons, plays an important role in insulin metabolism, and INSR knockout mice showed severe insulin resistance. Insulin resistance may interfere with follicle maturation and lead to PCOS by up-regulating pituitary LH secretion, membrane cell testosterone secretion and P450 scc activity in granulosa cells[19]. In the study on the correlation between the SNP variation of INSR gene and PCOS in Han people, rs2252673 is considered to be a low-risk indicator of PCOS[20]. A Saudi study claims that INSR rs1799817 is one of the susceptibility genes associated with PCOS, particularly in non-obese PCOS women. The hormonal changes of INSR and SNPS may play an important roles in the development of insulin resistance in PCOS patients[21]. There is an association between INSR genes and PCOS in studies conducted in different populations, regardless of ethnicity and race, and INSR may be a good genetic marker for PCOS. rs2059807 and rs1799817 in INSR gene are significantly correlated with insulin resistance in women with PCOS in different populations[22]. DNA methylation analysis suggests that the methylation of anti-Mullerian hormone receptor and INSR gene is related to the insulin resistance of PCOS, and their methylation levels are closely related to the pathogenesis of PCOS [23]. In a mouse model of PCOS, INSR expression was significantly increased after minocycline treatment. Since the expression of INSR gene was significantly increased in the minocycline receiving model group, minocycline and estradiol valerate may synergistically affect INSR gene and improve PCOS symptoms[24].
3.2 Insulin-like Growth Factor (IGF) Gene

The IGF system includes two ligands, IGF-1 and IGF-2, which regulate the growth, development, metabolism and other physiological processes of mammals through IGF-1 receptors. IGF-2 regulates human growth and development before and after birth and is expressed in many tissues, especially placenta[25]. The insulin-like growth factor binding protein (IGFBP) family has six members, named IGFBP1-IGFBP6, with molecular weights ranging from 24 to 45kDa. IGFBP plays an important role in prolonging the half-life of IGF in plasma and also inhibits the binding of IGF-1 and IGF-2 to their respective receptors. In a quantitative serum proteomic observational study of adolescent normal-weight women, women with PCOS had lower levels of IGF-1 and IGF-2, as well as IGFBP-2, IGFBP-3, and IGFBP-4, compared with healthy controls. This provides insights into the proinflammatory state and insulin dysregulation in serum proteomics in young women with PCOS and guides early intervention for PCOS[26]. However, in a Pakistani study, women with PCOS had insulin resistance and higher levels of IGF-1 than healthy women[27]. The high expression of IGF-2, platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) in PCOS patients will affect the pregnancy outcome, that is, the expression levels of PDGF, EGF and IGF-2 are independent risk factors affecting the pregnancy outcome of PCOS patients, and appropriate measures can improve the maternal and infant outcomes[28]. Phosphatidylinositol-3-kinase (PI3K) pathway is the key to the pathogenesis of PCOS. In the insulin-like growth factor 1 receptor (IGFIR) /PI3K pathway, IGFIR, insulin receptor substrate 1 and insulin receptor substrate 2 are significantly elevated in PCOS granule cells. However, the expression of phosphatase and tensin homologous (PTEN) was significantly reduced[29]. Overexpression of IGF-1 promotes cell viability and colony formation in granulosa cells. High concentration of insulin reduces the expression of miR-19b, stimulates the proliferation of granulosa cells, and increases the expression of IGF-1. Overexpression of miR-19b may be a potential treatment for PCOS[30]. In PCOS patients, miR-99a was significantly down-regulated, while IGF-1R was up-regulated. miR-99a can regulate IGF-1R after transcription. MiR-99a can reduce the proliferation of human granulosa cells and promote apoptosis by targeting IGF-1R. The down-regulation of miR-99a expression in PCOS patients may be closely related to insulin resistance and hyperinsulinemia. In addition, miR-323-3p also has similar functions in granulosa cells in PCOS, which partly explains the abnormal follicular formation in PCOS [31,32]. In a study of recombinant IGF-1 in a rat model of PCOS, it was demonstrated that IGF-1 may be a key factor in the pathogenesis of PCOS, and that the increase in androgens may be a pathological result rather than a cause of PCOS, due to the limited ability to detect IGF-1 in the hypothalamus. The hypothalamus and IGF-1 in vitro experiments need further study in the future[33]. Elevated serum IGF-1 levels may not be the main cause of the pathogenesis of PCOS. Body mass index may be a major determinant of serum IGF-1[34]. However, experiments have also shown that serum levels of IGF-1, IGF-2, and IGFBP-3 in obese PCOS women do not differ from those detected in non-obese PCOS women. IGF-1 is negatively correlated with metabolic parameters, and low IGF-1 may be an important predictor of metabolic syndrome in women with PCOS [35]. The results of different studies may be affected by sample size, race, etc., but all of them indicate that IGF-induced insulin resistance and hyperinsulinemia are closely related to PCOS. Currently, studies on IGF gene's involvement in PCOS have been conducted in cells, animals, and serum, which adds more theoretical basis for the correlation between the two. miR-19b, miR-323-3p and miR-99a are novel and promising molecular targets, which are expected to be used to improve the dysfunction of granulosa cells in PCOS for therapeutic purposes.

3.3 THADA Gene

THADA encode thyroid adenoma-related proteins, which are widely expressed in pancreas, adenal medulla, thyroid, adrenal cortex, testis, thymus, small intestine and stomach; Chromosomal aberrations in genomic regions containing THADA have been observed in benign thyroid adenomas. SNPS in THADA are also associated with diabetes [36]. Over the years, THADA has been identified as a candidate gene for PCOS. Previous GWAS evidence showed that patients with THADA rs12478601 CC genotype had increased miscarriage rates and oocyte counts, but decreased clinical pregnancy rates. In genotype-phenotype correlation analysis, the THADA gene causes excess androgens in PCOS. However, THADA knockout mice failed to replicate these results obtained in humans[37]. In a meta analysis of genetic susceptibility of PCOS syndrome patients in an Asian population, THADA rs13429458, INSR rs2059807, and LHCGR rs13405728 of PCOS were significantly correlated [38]. THADA gene polymorphism may affect pregnancy outcomes, metabolic disorders and insulin resistance in PCOS patients, and the specific mechanism needs further study.

3.4 Obesity Gene (FTO) Gene

The human FTO gene is located on chromosome 16 and is expressed in a variety of tissues, particularly adipose tissue and specific regions of the brain and muscle, suggesting a potential role for the FTO gene in weight regulation. Of the several known SNPS of the FTO gene, the FTO rs9939609 variant is the most extensively studied, located within the first FTO intron, which has two alleles, A and T, the former of which is associated with an increased risk of obesity and type 2 diabetes. In a Sri Lankan study, FTO gene variant rs9939609 was associated with hyperandrogenemia and PCOS metabolism in women of Sri Lankan descent[39]. In the study on the association between FTO gene variation and the difference in PCOS susceptibility to obesity in PCOS women, except rs17817449, rs9939609, rs9930506 and rs1121980, the association between rs9939973 and rs8044769 and the risk of PCOS was proved. The association of BMI dependent FTO variants with PCOS was confirmed for the first time[40]. The role of FTO gene variation as a predisposing factor for PCOS was emphasized. In Asians, FTO rs9939609, MTHFR rs1801131, and MTHFR rs1801133 polymorphisms may be inducers of PCOS[41]. Serum adiponectin and leptin levels can be used as diagnostic markers for PCOS, and FTO rs9939609 gene polymorphism increases susceptibility to PCOS[42]. The association between FTO SNP rs1421085 and BMI was stronger in women with PCOS[43]. A study of FTO variants in polycystic ovary syndrome susceptibility and IVF outcomes in Chinese
women showed that FTO rs8050136 and rs1588413 were significantly associated with PCOS susceptibility, and women with this risk allele were often associated with obesity and ovulated less frequently and have higher implantation rates than women with other non-risk alleles[44]. Although most studies indicate that FTO gene is correlated with PCOS, there are some controversies, and some studies also claim that FTO is not correlated with PCOS[45].

4. Genes Involved in Inflammatory Cytokines Related to PCOS

4.1 Tumor Necrosis Factor (TNF-α) Gene

Patients with PCOS are often accompanied by chronic low-grade inflammation. TNF-α is an inflammatory mediator produced by immune cells and plays an important role in the body’s inflammatory response and immune regulation. TNF-α gene polymorphism is associated with gynecological diseases such as preeclampsia and endometriosis, and is also one of the key regulatory factors of inflammatory response [46]. In the investigation of chronic inflammation in peripheral blood and ovary of PCOS patients, lymphocytes, monocytes, eosinophils, high triglycerides and TNF-α were significantly increased in PCOS patients, and the ovaries of PCOS patients showed chronic inflammation and a large number of inflammatory cells [47]. On the one hand, it fully indicates that PCOS is also a chronic inflammatory disease, and on the other hand, it provides evidence for the significant increase of TNF-α in PCOS patients. The promoter 1031 (T/C) polymorphism of TNF-α gene is associated with PCOS in the Korean population, which can be used as a clinical biomarker for the diagnosis of PCOS and help to understand the pathogenesis of PCOS [46]. In an Iranian study, there was no significant difference between TNF-α gene rs 361525 polymorphisms and PCOS, but serum TNF-α levels were elevated in PCOS patients and positively correlated with homeostasis model assessment (HOMA) factors. Elevated LH/FSH ratio and insulin resistance HOMA increase the risk of PCOS, suggesting that TNF-α may indirectly promote the progression of PCOS [48]. The pathogenesis of PCOS is a complex multi-factor process, which is influenced by the interaction of genetic factors, endocrine abnormalities, chronic inflammation, insulin resistance and other factors. TNF-α has an effect on ovarian active status, follicle development, and ovarian hormone synthesis, and is also associated with insulin resistance and metabolic abnormalities in PCOS patients. The exact role of TNF-α in the pathogenesis of PCOS still needs further research and exploration.

4.2 Interleukin (IL) Gene

The chronic low-grade inflammatory state of PCOS is often overlooked in studies, and genes related to inflammatory cytokines are an important part of PCOS. IL is an important cytokine involved in inflammatory response, secreted by a variety of cells, closely related to immune regulation and inflammatory response, and is used in various cells, affecting cell proliferation, migration, differentiation, etc. At present, up to 39 members of IL have been discovered, named IL-1-IL-39 [49]. In PCOS, the influence of IL cannot be ignored. Many studies have proved that IL-6 and IL-8 are highly expressed in PCOS, which may be related to the chronic inflammatory state, abnormal ovarian function and metabolic disorders in PCOS patients. Because IL-18 plays an important role in ovulation, follicle development, and hormone production, IL-18 is also a risk factor for PCOS. Specific polymorphic variation of IL-18 gene may lead to overexpression of IL-18, thereby increasing inflammatory response and influencing the pathogenesis of PCOS. At the same time, IL-10 and IL-33 also play important roles in the ovary, but they are limited by low sample size and few studies on related animal models, follicular fluid and cell lines. Further research is needed to determine the exact role in PCOS[50].

5. Conclusion and Prospect

In summary, the etiology of PCOS is complex. Besides the genes described in this paper, there are quite a few genes involved in the pathogenesis of PCOS. While environmental factors and lifestyle habits are not ignored, genetic factors play a significant roles in PCOS, and multiple gene polymorphisms play an important role in PCOS. The influence of each gene is not unique, and may contribute to the development of PCOS, as well as ovarian ovulation dysfunction and other clinical phenotypes by affecting hormone level in the hypothalamici-pituitary-ovarian axis, metabolic disorders, insulin resistance, or chronic inflammation. The clinical manifestations of PCOS not only affect the health of female appearance and body, but also have extraordinary significance for the genetic aspects of future generations. Due to certain differences between different races, it has not been clearly confirmed that gene polymorphism can determine the pathogenesis of PCOS due to the influence of experimental conditions and sample size limitation. Strengthening the exploration of genetic polymorphism related to PCOS can provide ideas for further elucidation of the genetic mechanism of PCOS, and also provide new ideas for the prevention and treatment of PCOS.

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59