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Analysis of The Occurrence of Rs.11632698 SNP Of CYP11a1 Gene Involved In PCOD

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Abstract

Polycystic ovary syndrome (PCOD) is a widespread reproductive disorder that encompasses many associated health conditions and has an impact on various metabolic processes. PCOD is depicted by hyperandrogenism, polycystic ovaries, and anovulation. It increases the risk of insulin resistance (IR), type 2 diabetes, obesity, and cardiovascular disease. The etiology of the disease remains unclear, and the subjective phenotype makes a united diagnosis difficult among physicians. It seems to be a familial genetic syndrome caused by a combination of environmental and genetic factors. It can be linked with metabolic disorders in first-degree family members. PCOD is the cause of up to 30% of infertility in couples seeking treatment. Currently, there is no cure for PCOD. Despite the growing incidence of this syndrome, limited research has been done that encompasses the entirety of PCOD spectrum. In this work the redundancy of a particular SNP (rs11632698) of CYP11A1 has been checked in the target population of PCOD to check whether it can be used as a biomarker.

Keywords

Polycystic Ovary Syndrome, Hyperandrogenism, PCOD, CYP11A1, rs11632698

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INTRODUCTION

Polycystic ovary syndrome (PCOD) is a common reproductive and endocrinologic disorder found in 6-10% of the female population. The three main phenotype characteristics of this condition are hyperandrogenism, polycystic ovaries, and ovulatory dysfunction. This syndrome can also be associated with metabolic issues including obesity, insulin resistance (found in 60-80% of women with PCOD), hyperinsulinemia, and type 2 diabetes mellitus (T2DM). PCOD is associated with cardiovascular problems, neurological and psychological effects on quality of life (including anxiety and depression), and breast and endometrial cancers. As many as 20% of

women with infertility problems (including fecund ability and early pregnancy loss) have been diagnosed with PCOD. It is often called the most common cause of anovulatory infertility in women. There is no known cause of PCOD, however there has been evidence that shows both environmental as well as genetic factors play a role in the etiology.

Recently, there has been an increase in interest in the field of PCOD research. In the past five years, there have been thousands of articles published concerning the different aspects and relationships regarding PCOD. Despite the high and increasing incidence of PCOD among the population, there are several aspects that remain ambiguous. Few studies have been conducted that grasp PCOD in its entire complexity.

Despite increased attention to PCOD, one of the most vital aspects of this disease is still highly disputed upon - the diagnosis. The etiology of this disease has not been well understood. There is a fundamental need for more research regarding the pathogenesis of PCOD in order to identify the underlying causes. An increasing number of publications infer that genetics is the primary factor of this disease, and take unique approaches to understand this genotypic-to-phenotypic association. Genetic abnormalities have been shown to play a significant role in the metabolic complications (including IR), and appear among both male and female first-degree relatives of women with PCOD. However, genetic research in PCOD is still new, and previously published findings need to be re-evaluated. There are several inconsistencies among genetic studies regarding PCOD[1].

The genetic evaluation of PCOD is also the gateway to many other novel areas of research. Since researchers are perplexed by the rapid evolution of the disease, the identification of genomic loci would give considerable insight[2].

The connection between PCOD and male relatives, a contentious topic, could be better understood with the advancement of genetic analysis. These two areas require a fundamental basis upon which to build theories in order to expand our knowledge on the etiology of the disease. These discoveries would also help create a novel treatment or cure.

The indefinite diagnostic criteria in addition to its immense intricacy make PCOD a challenging area of research.

LH Secretion

LH hypersecretion is a characteristic hallmark of PCOD. LH is secreted in a pulsatile manner. Women with PCOD have an increase in both the LH pulse frequency and amplitude, resulting in increased 24-hour secretion. This increase in LH secretion is thought to occur as a result of increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. Increased LH, in turn, leads to an increase in androgen production by the theca cells within the ovary.

Hyperinsulinemia and Insulin Resistance

Insulin resistance, defined as reduced glucose response to a given amount of insulin, is a characteristic metabolic disturbance associated with PCOD. Both obese and non- bese women with PCOD have a higher incidence of insulin resistance and hyperinsulinemia than age-matched controls; however, obese women with PCOD have significantly decreased insulin sensitivity compared with non-obese women who have PCOD[3].

Androgen Excess

The increase in LH, together with hyperinsulinemia, leads to an increase in androgen production by ovarian theca cells. The most likely primary factor driving the increase in testosterone secretion in PCOD is an increase in ovarian enzymatic activity involved in the synthesis of testosterone precursors[4].

1.1 The signs and symptoms include having:

i. Irregular menstrual periods, which means having period more than once a month or every few months, or never having period
ii. Periods that are very heavy or very light
iii. Unwanted hair growth on face, chest, back, hands, upper arms and legs, or around nipples
iv. Acne
v. Thinner hair on head.
vi. Patches of dark, thickened skin on neck, armpits, or between breasts.
vii. Weight problems
viii. Teens and women with PCOD also are at higher risk for type 2 diabetes, high blood pressure, and/or high cholesterol.

1.2 Prognosis and Diagnosis of PCOD

There are several challenges in confirming the diagnosis of PCOD in women who present its characteristics symptoms. Although hyperandrogenism testing is the most promising

diagnostic criteria, as it is seen in 60% of women with PCOD, its methods of assessment could result in diagnostic inconsistency.

The dilemma with the presence of hirsutism is that it is difficult to create a distinct profile of characteristics associated with PCOD. Clinically, hyperandrogenism is most often diagnosed through the presence of hirsutism. Other indicators such as acne and alopecia are occasionally taken into account. However, the biggest drawback of using hirsutism as a primary indicator of PCOD is its subjective assessment. It has been shown that women of different ethnicities display varying degrees of hirsutism, and symptoms are especially rare in Asian women and not well understood in adolescent patients.

The second test to diagnose hyperandrogenism is to measure circulating androgen levels. Measurements of serum total testosterone (T) and sex hormone binding protein (SHBG) are often the markers for these tests.

However, tests measuring androgens can be inaccurate/yield unreliable results. The accurate identification of hyperandrogenism in women is crucial to the overall diagnosis of PCOD. Since such a high percentage of PCOD patients display hyperandrogenism [6].

Genetic Background

There has been an increase in the hypothesis for a genetic predisposition to PCOD. Many recent studies have suggested that a genetic defect in a post-receptor insulin signal transduction can be linked to PCOD patients. This mutation can increase rates of insulin resistance and type 2 diabetes in first-degree relatives that are both male and female as well as twins. The vast complexity of phenotypic heterogeneity associated with PCOD complicates the focus of genetic studies.

Currently, there have been many candidate gene association studies on PCOD phenotypes. These studies are easier to perform than case-control cohorts, but they do not yield consistent results and lack sufficient sample sizes. Many of these studies include the investigations on the insulin gene (*INS*), the insulin receptor (*INSR*), and sex hormone-binding globulin (*SHBG*).

Ultrasonography in PCOD

Currently, the sonographic assessment of ovaries is one of the obligatory criteria in the diagnosis of PCOD. The influence of the development of new technologies in the sonographic assessment of PCO features is undoubtedly noticeable. This process has caused an increase in the percentage of diagnoses of PCO and PCOD. It is therefore needed to prepare new commonly accepted diagnostic norms concerning the number of ovarian follicles and the standardization of the technique in which they are counted. However, the application of new examination techniques does not entail the need for the modification of diagnostic norms concerning ovarian volume, which are characterized by lower sensitivity compared with ovarian follicle count. Attention is paid to the need of determining diagnostic norms depending on patients' age and ethnic origin in individual populations of women. The assessment of AMH levels as an equivalent of ultrasound features of PCO is a promising method. However, analytic methods have to be standardized in order to establish commonly accepted diagnostic norms. That is why, further studies, conducted on appropriately selected populations of women, are needed to investigate this non-uniform disease entity.

Obesity

Much like PCOD, obesity has become a recent worldwide epidemic in the past decades, especially in developed countries. The highest rates of obesity in PCOD patients occur in the United States and Australia, where 61-76% of women with PCOD meet the criteria for obesity.

It has been established that the pathogenesis of PCOD likely has the influence of genetics, in addition to environmental factors such as diet and lifestyle. Studies unrelated to PCOD have shown that hyperandrogenism is associated with obesity during the onset of puberty. If hyperandrogenism can be prevented by weight loss in prepubescents, it is possible that PCOD could be better maintained or even prevented in adult life[9].

Obesity not only intensifies the pre-existing PCOD phenotypes, but also projects poor treatment outcomes. Women seeking infertility treatment who have a high BMI are most likely to seek medical assistance for infertility. Lower rates of successful ART procedures are found among women with a high BMI, with an increased need for extended ovarian stimulation. In addition to this and the effects of the

PCOD phenotypes, there is an amplified risk of miscarriage in patients with a BMI over 25kg/m2.

Treatment

Unfortunately, PCOD cannot be cured. It can, however, be managed to a large extent by controlling symptoms. Exercise and a healthy diet are the best bet for women with PCOD as this will help to regulate their menstrual cycle and lower blood glucose levels.

High-fibre foods can help combat insulin resistance by slowing down digestion and reducing the impact of sugar on the blood. This may be beneficial to women with PCOD. Great options for high-fibre foods include broccoli, cauliflower and sprouts, red leaf lettuce, green and red peppers, beans and lentils, tomatoes, spinach, almonds and walnuts, olive oil, fruits, such as blueberries and strawberries, and fatty fish high in omega-3 fatty acids, such as salmon.

Lean protein sources like tofu, chicken and fish don't provide fibre but are filling and a healthy dietary option for women with PCOD.

Instead of three big meals they should have five small meals, which helps metabolize food and in maintaining weight.

If women with PCOD are suffering from infertility, then fertility drugs may be administered to aid ovulation. On the other hand, if a woman does not want to get pregnant, then birth control pills may be prescribed.

In order to stop excess hair growth and help reduce acne, using anti-androgens is the recommended course of action. While many women have been recommended to regularly exercise, (minimum 45 minutes a day, five times a week) one refrain that we commonly hear is that they don't have time. Up to 5-10 per cent of weight loss will help improve the symptoms, hormonal balance and regularization of menstrual cycle. PCOD among women, especially adolescents, is an urgent public health problem that needs careful assessment, timely intervention and appropriate treatment.

Promotion of healthy lifestyles, the need for regular exercise and increased awareness programs on PCOD is the need of the hour to enable a holistic solution to this problem.

STEPS INVOLVED IN THE PROCESS

i. Sample Collection (Diseased & Controlled)
ii. Blood (Genomic) DNA Isolation
iii. Purification & Storage
iv. Agarose Gel Electrophoresis
v. Selection of Target Gene
vi. Selection of Target SNP
vii. Primer Designing
viii. PCR Amplification
ix. Sequencing
x. MSA (Multiple Sequence Alignment) for SNP Identification

CONCLUSION

As per the above study, the results shows that out of all the 12 diseased samples 3 were found with a mutation within a single base pair within the specific region, hence we arrived a conclusion that the SNP that was subjected to study could offer a chance in the involved in PCOD. In order to select this SNP as a Biomarker a wider study is recommended.

There are chances for the influence of other factors too, like other SNPs', Environmental factors and so on.

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