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Review

Identifying genes associated with the development of human polycystic ovary syndrome

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ABSTRACT

The pathophysiology of polycystic ovary syndrome (PCOS) is confusing until today as it is a multifactorial endocrine disorder. It is presented with altered gonadotropin levels, bulky multi-follicular ovaries, infertility, and obesity. This complex pathophysiology is linked with insulin resistance and hyperandrogenism. Hyperandrogenemia significantly contributes towards cosmetic anomalies including hirsutism, acne, and alopecia in the PCOS women. The preexisting insulin resistance in women with PCOS is likely to aggravate the increased levels of androgen. The review findings have shown that in the steroidogenic pathway, ovarian steroidogenesis patterns classify mainly towards the hypertrophy of theca cells along with alteration in the expression of key enzymes. The association of polymorphisms in genes encoding the process of an intricate cascade of steroidogenesis is delineated. The emergence of an unanimously accepted genetic marker for susceptible PCOS was affected based on inconsistent findings. The present study has provided a comprehensive summary of the impact of polymorphisms among the common androgen-related genes to govern the genetic predisposition.

Contents

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1. Introduction

Polycystic ovary syndrome (PCOS) has affected the majority of women across the world and occurred in approximately 6–10% of the pre-menopausal women (Goodarzi et al., 2011; Dadachanji et al., 2018). Significant biomarkers of PCOS include chronic anovulation, increased androgen levels, distorted gonadotropin ratios, irregular menstrual cycles, the appearance of polycystic ovarian morphology, and insulin resistance (Teede et al., 2010). Women suffering from PCOS are likely to develop metabolic syndrome, type II diabetes mellitus, and cardiovascular disease (CVD) in the long-run. The significant drivers including insulin resistance and androgen excess, extend the metabolic and reproductive consequences of the affected women; however, there is no emergence of a clear-cut origin that underlines its pathophysiology. The intense ovarian steroidogenesis develops because of cell hyperplasia, which is attributed to the fact that the primary source of hyperandrogenism among women with PCOS is an ovary. Anovulation is promoted as a result of hyperandrogenism that develops because of the follicular arrest. There is a significant association of reduced maturation rats and oocyte developmental competence with increased levels of androgen (Dadachanji et al., 2018). Moreover, another study has found a significant correlation between embryo development, fertilization, and miscarriage with testosterone (Qiao and Feng, 2010). Defects in common steroid pathway biosynthesis enzymes and cortisol metabolism result in excess of adrenal androgen that is found among 20–30% of the women (Goodarzi et al., 2015). Hyperandrogenemia is responsible for predicting the severity of the cardiovascular risk and cardio-metabolic profiles, apart from modifying the reproductive outcomes (Daan et al., 2014). The incidence of metabolic syndrome, indices of insulin resistance, and dyslipidemia are affected as a result of unfavorable hyperandrogenemia (Yang et al., 2016). The association of genes involved in the development of PCOS has been investigated earlier. However, the present study has mainly focused on the association of genes involved in the development of PCOS.

1.1. Steroid metabolism

The principal organ that maintains the physiology of the female reproductive system is ovary as they are responsible for developing ovarian follicles, synthesis of steroid hormone, and production of mature oocytes (McGee and Hsueh, 2000). The process of converting precursor cholesterol to biologically active steroid hormones is known as steroidogenesis. The biosynthesis of hormones including progestins, estrogen, mineralocorticoids, androgens, and glucocorticoids is performed by the steroidogenic enzymes that comprise steroid reductases, specific cytochrome P450 enzymes (CYPs), and hydroxysteroid dehydrogenases (HSDs). The steroid producing organs and tissues contain CYP11A that is bounded to the inner membrane of mitochondria. Conversion of cholesterol to pregnenolone by CYP11A (cholesterol side-chain cleavage) results in the initiation of de novo synthesis of all steroid hormones (Dadachanji et al., 2018). The precursors for all other steroid hormones are formed by pregnenolone and progesterone. Steroidogenesis taking place within the ovary is a well-regulated process and it is governed by the gonadotropins and signaling mechanisms arising in the ovarian cells. There is the conversion of pregnenolone to dehydroepiandrosterone (DHEA) and progesterone to androstenedione as a result of androgen synthesis taking place in the thecal cells having receptors for luteinizing hormone. The CYP19 aromatase enzymes present in the Follicle-stimulating hormone (FSH) acts in the androgens to stimulate the granulosa cells to estrogens that play an important role in the normal functioning of the ovary.

1.2. Pathophysiology of PCOS

Excess of androgen in females results in the development of PCOS (Diamanti-Kandarakis et al., 2006). The increased secretion of luteinizing, as compared to the follicle-stimulating hormone is favored by increased gonadotropin-releasing hormone (Diamanti-Kandarakis et al., 2006). The expression of a steroidogenic acute regulatory protein (StAR), cytochrome P450c17 (CYP17), P450 side-chain cleavage (P450scc), and increase steroidogenic activity in the theca cells results in the production of androstenedione, under the control of the increased release of luteinizing hormone (Diamanti-Kandarakis et al., 2008). The follicle-stimulating hormone released from the pituitary gland facilitates the conversion of androstenedione into estrogen by aromatase. However, the follicular development is impaired and aromatase activity is reduced, when the release of the follicle-stimulating hormone is deficient causing excess accumulation of androgen and hyperandrogenemia in PCOS women.

There are numerous follicles in the polycystic ovaries that are trapped in the preantral and antral stages with an accumulation of follicular fluid and thecal hyperplasia, which results in the formation of cyst-like structures. The ovaries of PCOS women enlarge because of increased ovarian stromal volume due to the increased number of fluids filled follicles. The steroid inducing action of luteinizing hormone is intensified as a result of insulin resistance that worsens hyperandrogenemia and increases luteinizing hormone (LH) pulse amplitude, indirectly. Hyperandrogenemia is exacerbated as a result of indirect action of insulin that increases the free and bioavailable testosterone levels and reduces hepatic biosynthesis of sex hormone-binding globulin (Diamanti-Kandarakis et al., 2008). The sequence of hyperinsulinemia followed by hyperandrogenemia promotes the environment with hormonal imbalance (Diamanti-Kandarakis et al., 2008). There is a continuous increase in the androgen pool because of coupling between the diminished conversion of testosterone to estrogen and lowered aromatase activity. There are marked changes in the methylation status of essential genes that are induced by follicular hyperandrogenemia for reproduction and development such as Peroxisome proliferator activated receptor gamma (PPARϒ), Nuclear receptor co-repressor 1 (NCOR1), and Histone deacetylase 3 (HDAC3) (Qu et al., 2012). The heterogeneity in androgenic phenotype in the steroidogenic pathway may be attributed to differential activity of important enzymes because of increased activity of both 17 and 20 lyases in the 3β-hydroxysteroid dehydrogenase II (3β-HSD) and Δ4 pathway combined with low aromatase activity was documented in hyperandrogenic PCOS women (de Medeiros et al., 2015).

1.3. Genetics of PCOS

The clustering of PCOS within families provides evidence for its strong genetic component or PCOS like features among the relatives of the affected individual woman (Goodarzi et al., 2011). The contribution of heritability of this disorder has been explained based on the approaches used in the twin and linkage studies. A strong association between follistatin and Cytochrome P450 Family 11 Subfamily A Member 1 (CYP11A1) gene in affected siblings with hyperandrogenemia and PCOS related traits was predicted by studying 37 candidate genes. Moreover, the transmission disequilibrium test presented a strong genetic association between the D19S884 allelic marker located near the INSR gene and the development of PCOS (Dadachanji et al., 2018). The significance of genetic predisposition in manifesting PCOS is highlighted through the candidate genes showing involvement in the pathways that relate to etiology and associated anomalies of the syndrome (Prapas et al., 2009). Insulin signaling, chronic

inflammation, regulation of gonadotropin, and energy homeostasis have been characterized as polymorphisms of the genes involved in different pathways; however, there is no information related to the exact roles of the susceptible genes (Prapas et al., 2009).

Functional changes are revealed through single nucleotide polymorphisms because of variation in amino acids, candidate gene approaches, and modulation of gene expression. The presentation of functional changes helps to decipher the effect of differential frequency distribution among the diseased and healthy individuals. The study related to PCOS genetics has been revolutionized through genome-wide association studies; whereas, candidate gene approaches have been studied in smaller populations. In line with the genes involved in balancing action and regulation of insulin, and susceptibility and related traits of PCOS (Shaikh et al., 2014), the present study has mainly focused on the gene polymorphisms associated with the development of PCOS.

1.4. CYP11A1 gene

The gene CYP11A1 present on chromosome 15q23-24 is responsible for encoding the enzyme P450. This enzyme plays a major role in catalyzing the rate-limiting step (conversion of cholesterol to pregnenolone) in ovarian steroidogenesis (Pusalkar et al., 2009). An increase in expression of CYP11A, in comparison to the normal theca cells, demonstrate the propagation of theca cells that are derived from ovaries through long-term culture (Wickenheisser et al., 2012). CYP11A locus is involved in the development of PCOS as it shows the association of PCOS development with repetitions in the sequencing of 5′UTR (TTTTA). Previous studies conducted in different corners of the world have shown a positive association between pentanucleotide repeat alleles and susceptibility of PCOS (Daneshmand et al., 2002; Gaasenbeek et al., 2004; Reddy et al., 2014). The risk of PCOS in Chinese women was demonstrated by Wang et al. (2006), demonstrating different allele combinations that either increase or decrease the risk of developing PCOS among the women population. The association of increased risk of developing PCOS and repeated polymorphisms of CYP11A was confirmed by Shen et al. (2014).

Another study conducted by Yu et al. (2014) indicated that a total of 6 repeats decreased the development of PCOS considering the dominant; whereas, considering the recessive model carriers of 4 repeats increased the development of PCOS. The previous study has shown the presence of testosterone in an increased amount among women with PCOS, who are already the carriers of short alleles (Pusalkar et al., 2009). On the contrary, some of the studies have shown no impact of allele doses on the transcription of the CYP11A gene (Gaasenbeek et al., 2004; Li and Guijin, 2005). There is a significant and positive impact of metabolic traits such as decreased AUC glucose values, decreased FSH values, obesity, alleviated dyslipidemia, and increased waist-hip ratio on an increase of repeated polymorphisms (Hao et al., 2009; Prazakova et al., 2010). A polymorphism named rs4077582, along with the alteration in the levels of LH and testosterone showed significant association among women suffering from PCOS (Zhang et al., 2012). The analysis of the above discussed studies proves CYP11A to be a promising genetic biomarker among women with PCOS.

This gene is composed of 10 exons and located on chromosome 15q24.1. Polymorphism is identified as another genetic predispose to PCOS in the promotor pentanucleotide (TTTTA)n. It is observed that CYP11A polymorphism is considered as a risk molecular marker for PCOS. When there is an association between environmental factors and genetics, the risk increases. A study carried-out regarding 15 allele variations varying from 2 to 16 repeats and the 8 repeat alleles were commonly reported. This study has indicated the presence of >8 repeat alleles in PCOS influenced females, which refers to 3-fold risk for PCOS predisposition as compared to control (Reddy et al., 2014). Another study has shown that PCOS is caused by a polymorphism in CYP11A. PCOS is associated significantly with SNP rs4077582 in CYP11A and it further increases androgen levels using the hormone regulation in different genotypes (Zhang et al., 2012).

1.5. CYP17 gene

CYP17 gene is responsible for coding cytochrome P450 enzyme at chromosome 10q24.3. This enzyme is involved in a 17-hydroxylase activity that converts progesterone into 17-hydroxyprogesterone and pregnenolone into 17-hydroxypregnenolone. These steroids are converted to dehydroepiandrosterone (DHEA) and 4-androstenedione via 17,20-lyase activity (Prapas et al., 2009). An additional Sp1 transcription factor binding site that regulates the expression of CYP17 and consequently androgen levels are created at −34 position (−34 T/C) in the promoter resulting in polymorphism. Except for Indian women (Pusalkar et al., 2009), the polymorphism occurring in this gene was not found significant in the development of PCOS among women from different regions (Park et al., 2008; Chua et al., 2012; Li et al., 2015). The study conducted by Pusalkar et al. (2009) showed that there is an increased frequency of C allele among Indian women suffering from PCOS that is likely to affect the hyperandrogenic phenotype among them. There is a negative impact of this polymorphism on certain metabolic traits such as insulin resistance, obesity, and waist circumference (Techatraisak et al., 2015). Considering the genetic model or stratification showed no association of this variant with an increased risk of developing PCOS. However, an increased risk of developing PCOS was observed through the dominant genetic model. This difference may be due to different sample sizes used in different studies across different parts of the world (Li et al., 2012).

It was also addressed that polymorphism in CYP17 leads to an upsurge in insulin resistance, excessive lipid, and body weight due to the defect found in the gene after performing restriction fragment length polymorphism (RFLP) PCR. Therefore, it is related to metabolic pathways along with PCOS. T/C polymorphism was also reported among the Chinese population in the CYP17A in another study. TC, TT, CC genotype was depicted from the genetic and clinical parameters, which was 43.71%, 49.69% and 6.6%, respectively. Affected females having CC genotype had increased testosterone than individuals who have TC, TT genotype.

1.6. CYP19 gene

The CYP19 gene presents on chromosome 15q21.2 encodes the aromatase p450 enzyme that plays an important role in synthesizing estrogens from androgens (Dadachanji et al., 2018). There is a decrease in aromatase activity among lean and obese women suffering from PCOS that may be further inhibited by hyperandrogenemia (de Medeiros et al., 2015). PCOS women are presented with increased levels of testosterone in a follicular fluid as the result of decreased aromatase expression concomitant (Yang et al., 2015). The suppressed expression of aromatase was because of hypermethylation of the promoter, decreased protein levels, and reduced CYP19A1 Messenger ribonucleic acid (mRNA) (Yu et al., 2013). A study conducted by Jin et al. (2009) showed a significant association of intronic variant rs2414096 with an increased risk of developing PCOS among the women. The adolescent girls with this polymorphism are observed to have increased PCOS symptom scores along with changes in the circulating concentrations of testosterone and estradiol. Another study undergoing a treatment regime of oral contraceptives in ovulatory and anovulatory PCOS women for 6 months showed an insignificant association of rs2414096 polymorphism with PCOS (Maier and Spritzer, 2012).

The tetranucleotide repeat polymorphism is known as a common polymorphism occurring in the fourth intron and is associated with suboptimal aromatase activity (Xita et al., 2010). Previous studies have demonstrated a predominance of the short allele repeats that mainly comprise of seven repeats (Xita et al., 2010; Hao et al., 2010; Lazaros et al., 2013). There is a significant association of these short-repeated alleles with certain hormonal parameters that include increase of luteinizing hormone, testosterone, and follicular stimulating hormone; however, there is a reduction in reproductive markers such as the total oocyte count and number of large follicles (Xita et al., 2010; Lazaros et al., 2013). Following the assisted reproductive technique intervention, these alleles are likely to predict successful pregnancies (Lazaros et al., 2013). The lipid metabolism is influenced among the PCOS women, who are carriers of 11 repeat alleles (Hao et al., 2010). A study conducted by Zhang et al. (2012) investigated polymorphism known as rs2470152 and found that it does not increase the risk of PCOS; however, there was a significant association of heterozygous TC genotype with increased levels of testosterone concerned with the regulation of aromatase activity (Zhang et al., 2012). PCOS susceptibility is affected as a result of an increase in the aromatase activity because of a missense polymorphism in Arg264Cys. Therefore, the CYP19 gene is presented with a significant role in the PCOS outcome.

There is an inclined risk of other conditions such as prostate cancer, endometrial cancer, and breast cancer due to polymorphism in the CYP19A gene, besides PCOS progression. Among the Korean population, SNP's identification was further reported to play an essential role in the estrogen pathway disruption. 19 variations have been identified, which are present in 4 exons, one single-nucleotide polymorphism (SNP) in 30 untranslated region (UTR), 6 SNP in 50 untranslated areas, and 10 introns. Rs700519 and two intronic regions rs60271534 and rs2414096 were found among the South Indian population SNP at exon region. PCOS is also caused by these variants (Reddy 2015).

1.7. AR gene

An androgen receptor (AR) protein is produced based on the instructions of the AR gene. Androgens are hormones that are essential for normal male sexual development prior to birth and during puberty. The body is allowed to be responded by AR to such hormones. The existence of receptors in a number of body tissues, where they are linked with androgens (Franks and Hardy, 2018). The activity of androgen-responsive genes is regulated by the resulting androgen receptor complex DNA. The AR assists in directing the development of male sexual characteristics by turning the genes on or off as required. In both males and females, androgen receptors and androgens have other essential functions such as sex drive and regulating hair growth.

The androgen receptor (AR) is coded by the AR gene that is located on chromosome X. This gene comprises of poorly conserved N terminal domain with polymorphic CAG repetitions (Peng et al., 2014). The number of CAG repeats and AR transactivation efficiency demonstrate an inverse correlation. For instance, one of the previously conducted case studies reported about a woman carrying heterozygous AR gene mutation, who gave birth to an infant suffering androgen insensitivity syndrome. This trait showed plausible consequences regarding the reproductive outcomes linked with mutations in the AR gene, rather than the length repetitions (Nam et al., 2015). The prime location of AR is within the granulosa cells of preantral and antral follicles, theca internal cells of preantral follicles, and theca and granulosa cells of dominant follicles (Walters et al., 2008). The prevalence of PCOS has been indicated through inconsistent associations among the differences in a number of cytosine-adenine-guanine (CAG) repeats in exon 1. Previous studies have demonstrated an increased frequency of short AR CAG repeats for PCOS cases (Wang et al., 2011; Xia et al., 2012; Lin et al., 2013).

The inherent hyperandrogenic phenotype appears as the result of increased AR activity and enhanced sensitivity of androgen in response to low levels of circulating testosterone, which promotes hirsutism, irregular menstrual cycles, and acne (Schüring et al., 2012). A significant trend of short CAG repeat lengths was observed among the anovulatory normoandrogenic PCOS women that resulted in increased sensitivity of intrinsic androgen. The difference in the presence of shorter repeat length among different populations indicates the possible role of ethnic variation. The women suffering from PCOS show CAG repeat lengths that are capable of modifying insulin and testosterone; although, they show no association with the increased risk of developing PCOS. The serum circulating testosterone levels are successfully predicted through CAG repeat polymorphism among the PCOS women (Peng et al., 2014). Increased level of testosterone aggravates the resistance of insulin among the PCOS women, which indicates the underlying mechanism of hyperandrogenemia induced insulin resistance through the putative effect of CAG repeats (Möhlig et al., 2006). Moreover, in comparison to fertile PCOS women, the infertile PCOS women are presented with preferential expression of long CAG repeat alleles. On the contrary, preferential expression of long CAG repeat alleles may also be observed among the infertile PCOS women in comparison to the fertile PCOS women. The association between CAG repeats lengths at AR and the development of PCOS were not considered as the determining factors in PCOS etiology. However, there is a significant association of gametogenetin (GGN) repeat polymorphism with and rs6152G/A polymorphism among the PCOS women (Zhang et al., 2013). Moreover, the hyperandrogenic phenotype may also be exacerbated through AR polymorphisms among the PCOS women.

The availability of androgen is the dependent factor for the cyclical production of estradiol in the form of a steroid precursor and often as cyclical changes in gonadotrophins. Androgens are produced by the theca cells of antral follicles under the effect of tonic levels of LH. LH receptors exist in theca cells, but usually appear in granulosa cells in mature follicles greater than 10 mm in diameter in the human ovary (He et al., 2018). Similarly, the granulosa cells also showed the presence of FSH receptors. Across the basal lamina, androgens diffuse to the granulosa layer where they are converted to estrogen by the action of CYP19 under the control of FSH (Prasasya and Mayo, 2019). Within the follicle, this coordinated interaction of gonadotrophins is usually considered as the 2-cell, 2-gonadotrophin process. Androgens also played a role in the decay of antral follicles that form part of the cohort that underwent additional growth with respect to the early follicular phase increased in FSH but revert in the late follicular phase as FSH levels fall (Chou and Chen, 2018). It is a physiological platform that assures that mono-follicular ovulation is the rule in humans. The ability of androgens to tempt atresia in antral follicles has usually been cast as a deleterious impact, specifically under androgen excess conditions. However, the role of androgens might be more nuanced as compared to the described.

There is sufficient evidence to portray that the growth of both antral and preantral follicles in different species is stimulated by androgens (Yang and Fortune, 2006; Qureshi et al., 2008; Laird et al., 2017). The importance of androgen action deems to be suitable for normal follicle function and development. The responsiveness of granulosa is also increased by androgen to FSH with respect to both the expression and growth of fundamental genes entailed in steroid genesis (Laird et al., 2017). It has been observed that the growth of both antral and preantral follicles is led by in vivo exposure to androgen and; therefore, was related to the escalated expression of FSH receptor in granulosa cells (Franks and Hardy,

2018). Ki67 was positively correlated with an AR expression but negatively correlated with apoptotic cell count.

In a normal cycle, the role of androgens has likely been exaggerated in causing follicle atresia. One of the major causes of atresia in subsidiary follicles is FSH deficiency in mono-ovulatory species, but androgen action may contribute to the follicle loss in these estrogen-deficient follicles.

1.8. SHBG gene

The synthesis of sex hormone-binding globulin (SHBG) takes place in the liver. The gene lowers circulating steroid hormones after binding to androgens and estrogen with increased affinity, which makes them available to the targeted tissues (Hammond, 2016). The plasma levels, plasma clearance efficiency, and hepatic biosynthesis are altered as the result of several polymorphisms in the SHBG gene that is located on chromosome 17 (Hammond, 2016). This alteration is responsible for regulating the distribution of sex steroid hormones. The women suffering from SHBG deficiency were presented with truncated SHBG synthesis and abnormal glycosylation, which decreased the SHBG levels in response to increased free testosterone concentration in blood circulation. The evidence of the association of longer TAAAA repeats with late-onset of menarche supports the putative genetic contribution of SHBG polymorphisms (Cousin et al., 2004).

SHBG is produced by the liver and associates to circulate sex steroids with high affinity as a transporter of sex hormones. It also regulates the concentration of bioactive sex hormones in the blood and influences their bioavailability (Hammond et al., 2012). It is an influential auxiliary predictor to determine the androgen level as SHBG portrays a low affinity for estradiol and high affinity for testosterone (Somboonporn and Davis, 2004). Biological effects are not resulted through the binding of testosterone by SHBG and only up to 3% of unrestricted free testosterone has biological activity. Thereby, the SHBG assess the therapeutic effectiveness of treatment and measure the severity of hyperandrogenism. It has been observed that SHBG is affected by insulin with hyperinsulinism preventing its secretion and synthesis (Lim et al., 2013). Serum SHBG levels are considerably decreased in patients suffering from hyperinsulinemia than healthy individuals (Tawfeek et al., 2017). In addition, low serum SHBG levels might be a risk factor for abnormal glucose metabolism. Generally, both serum SHBG and hormone levels must be considered in patients with PCOS, as they play an essential role in the growth and prognosis of PCOS in clinical practice.

Decreased levels of SHBG and increased levels of testosterone with raised free androgen index (FAI), dehydroepiandrosterone (DHEAS), and T/E2 ratios were demonstrated among the women with long SHBG alleles coupled with short CYP19 alleles (Xita et al., 2008). The metabolism of SHBG is affected as the result of functional missense polymorphism in exon 8 which results in a change of amino acid to asparagine from aspartic acid that delays the half-life of SHBG (Cousin et al., 2004). SHBG levels are also lowered by missense polymorphism of E326K in PCOS women without any involvement of androgen, body mass index (BMI), or insulin-related traits. Previous studies have demonstrated that metabolism of SHBG significantly depends on rs1799941 and rs727428 in SHBG gene (Wickham et al., 2011; Martínez-García et al., 2012); whereas, it had no association with the increasing risk of developing PCOS (Wickham et al., 2011).

Regulating SHBG concentrations are typically low in PCOS patients as these women have augmented androgen levels and usually present with compensatory hyperinsulinemia and insulin resistance. Similarly, the hepatic synthesis and secretion of SHBG are inhibited by both androgens and insulin. Excessive androgen is an important aspect of PCOS, and it is also an extreme reason for infertility in PCOS women. The ovaries and the adrenal gland mainly produce excess androgens in these women, which inhibit the growth of the selective follicles and lead to a large amount of follicular atresia and consequently cause ovulation disorders (Jonard and Dewailly, 2004). This is the major cause of anovulation in PCOS patients with hyperandrogenism. Serum androgen levels were reported to be an autonomous risk factor for metabolic syndrome in PCOS adolescent girls (Coviello, Legro and Dunaif, 2006). Similarly, IR is positively correlated with androgen levels in patients with PCOS as hyperandrogenism exhibits IR by increasing lipoprotein and mitigating insulin clearance (Shorakae et al., 2018). Consequently, compensatory hyperinsulinemia worse hyperandrogenism (Nestler et al., 1998). Binding free androgens to reduce hyperandrogenism and IR assists in lowering free androgen levels via SHBG.

Testosterone is considerably augmented in patients with PCOS than healthy individuals. However, testosterone is negatively correlated with SHBG levels. Testosterone in HepG2 cells inhibits SHBG production even though the mechanism was not explained. Serum SHBG levels reduce with increasing testosterone levels as boys enter puberty. Similarly, SHBG can be inhibited by exogenous androgens even at low doses (Handelsman, Sikaris and Ly, 2016). In PCOS patients, hyperandrogenemia is one of the causes of the low serum level of SHBG. The SHBG expression can be affected by the androgen signaling pathway through regulation of other factors as the human SHBG promoter does not comprise androgen-binding elements (Shahebrahimi et al., 2016).

It should be noted that a low serum SHBG level is not only an essential influencing factor for hyperandrogenemia in patients with PCOS, but it is also an essential indicator of insulin resistance and a risk factor for lipid metabolism and glucose disorders. Complications and long-term prognosis in PCOS might be associated with serum SHBG and it plays an essential role in the PCOS pathogenesis. A binding site for HNF-4α is contained within the SHBG promoter, which links to this site for improving the gene's transcriptional activity.

1.9. StAR gene

StAR gene is responsible for encoding the steroidogenic acute regulatory protein. The binding of this protein results in binding and facilitation of cholesterol in the mitochondria to induce steroidogenesis. This gene is present on chromosome 8p11.2; however, one of the previous studies has shown an insignificant association of polymorphism of this gene with increased PCOS risk.

The objective of PCOS treatment is to restore ovulation. Aromatase inhibitors are the drugs used in PCOS treatment such as letrozole, which binds with gonadotropins for improving clomiphene citrate and ovulation, which is the initial treatment for encouraging ovulation of patients with PCOS who are undergoing intrauterine insemination. Metformin and recombinant follicle-stimulating hormone are prescribed as insulin sensitizers. A heterogeneous syndrome (PCOS) is produced by a different diagnosis of PCOS markers and different responses to treatment due to individual pharmacogenetic elements (Overbeek and Lambalk, 2009).

It has been observed that patients with PCOS have an irregularity in androgen biosynthesis, which results in hyperandrogenemia (Overbeek and Lambalk, 2009; Kahsar-Miller et al., 2001). It is considered as an initial step in androgen biosynthesis to transport cholesterol via the StAR protein from outer to the inner mitochondrial membrane (Barbar, LeHoux and Lavigne, 2009; Miller, 2007). The central nervous system, gonads, adrenal glands, and placenta are regions for synthesizing steroid hormones. Cholesterol is a common precursor of all steroid hormones irrespective of the areas that are synthesized by steroid hormones. The delivery of cellular

cholesterol from the outer to the inner mitochondrial membrane is the first limiting step of steroidogenesis where the cytochrome p450 side-chain cleavage enzyme is present (Nazouri, et al., 2015).

There are 284 cloned and highly conserved amino acids comprised of StAR protein in many species such as amphibians, fish, birds, and mammals (Miller, 2007; Strauss et al., 2003). Testis, kidney, ovary, and adrenal cortex are human tissues found in StAR mRNA and insulin-like growth factor, GATA enhancer-binding protein, GATA-4 and steroidogenic factor 1 are considered as StAR protein regulators (Barbar, LeHoux and Lavigne, 2009). It is located in the region 8p11.2 on the short arm of chromosome 8. StAR encourages and starts the process of steroidogenesis as it has an extreme role in binding to cholesterol. However, findings have indicated that patients with PCOS consist of high levels of steroid hormones so it may result in the abnormality of steroidogenesis found in the PCOS patients. The most mutations were the variations located between exons 5 and 7 in the StAR gene.

1.10. HSD17B5 gene

The conversion of androstenedione to testosterone in theca cells and adrenal glands is assisted by enzyme type 17 β-hydroxysteroid dehydrogenase type 5 (HSD17B5) (Ju et al., 2015). Qin et al. (2006) revealed the polymorphism in the promoter region through the investigation of its prevalence in a population of ethnically diverse women suffering from PCOS. Qin et al. (2006) showed that the gene is responsible for modulating the biosynthesis of testosterone imposing significant influence on the levels of plasma testosterone. Testosterone levels are affected by intronic polymorphism rs12529, but there was no impact on the risk of PCOS. On the contrary, rs1937845 increased the risk of developing PCOS along with increased testosterone levels and homeostasis model assessment of β -cell function (HOMA-B) index (Ju et al., 2015). The women may be attributed to a treatment regimen with oral contraceptive pills to improve their hyperandrogenic phenotype; however, this treatment could not be applied in the case of HSD17B5 polymorphisms (Maier et al., 2012).

HSD17B5 is a member of the Aldo-keto reductase superfamily, which consists of several multifunctional enzymes that vary between their substrate specializations and tissue-specific expression profiles (Qin et al., 2006). The enzyme responsible for the reduction of androstenedione is encoded by HSD17B5 in theca adrenals and ovarian cells, which are the main features of testosterone in women (Goodarzi et al., 2008). It is an applicant gene to be examined for the hyperandrogenemia in PCOS. The occurrence of PCOS has rapidly increased recently with the modifications in the living environment as well as in social pressure. Hyperandrogenism is a typical clinical manifestation of a patient with PCOS among the complex clinical features. Anovulation, menstrual disorders, infertility, and follicular atresia are caused by hyperandrogenism. In addition, it can lead to hairy and greasy skin, hair loss, and acne.

The common DNA sequence variations among the population are polymorphisms that play an integral role in the development of several hereditary diseases. HSD17B5 is a vital gene in androgenic metabolism. It is noted that HSD17B5 plays an essential role in the incidence of hyperandrogenemia in PCOS patients and might be related to insulin resistance. HSD17B5 might be considered as a candidate gene for the PCOS etiopathogenesis. It is probable that the variation of the sequence might change the expression or the function of the signal pathways.

1.11. INSL3 gene

Insulin-like factor 3 (INSL3) is a novel circulating peptide hormone of the relaxin-insulin family. It is a major secretory product of the testicular Leydig cells in male mammals including humans. Insulin-like factor 3 is located in the corpus luteum of the ovary and the thecal cells. The role of INSL3-RXFP2 was established by Glister et al. (2013) to maintain the production of androgen by ovarian theca cells. Increased levels of INSL3 have been reported by women suffering from PCOS. An important role is played by INSL3 polymorphisms in the modulation of ovarian steroidogenesis, which significantly contributes to the pathogenesis of PCOS. The metabolic and hyperandrogenemia related traits of PCOS in both controls and women with PCOS are affected by region polymorphisms along with the rs6543 SNP, depending on the physiological state (Shaikh et al., 2016).

INSL3 is also synthesized in the corpora lutea and ovarian stroma, and in the theca interna cells of antra follicles (Ivell et al., 2005). INSL3 expression dynamically changes with follicle development by the theca interna of bovine follicles along with INSL3 levels. PCOS influence ovaries characteristically in the form of the cortical stroma and the theca interna. These follicles are not atretic rather their growth is prematurely congested, which results in the failure of dominant follicle ovulation and development (Jonard et al., 2003). They are positively associated with the ovarian androgenic function as evaluated by the serum-free testosterone response to ovarian steroid responses to nafarelin and a dexamethasone-androgen suppression test. Furthermore, LH levels above the normal range are found among the majority of the PCOS women. On the other hand, this condition is assumed to be specifically evident in normal-weight as compared to obese PCOS women, which relies on mitigated LH pulse amplitude and LH response to GnRH (Silfen et al., 2003).

In PCOS, increased LH levels are commonly observed, specifically in normal-weight individuals. On the contrary, the presence of obesity markedly distributes LH pulsatile secretion. Thereby, lower LH concentrations are significantly characterized by PCOS women with excess body weight as compared to the normal-weight counterparts in order to resemble the normal range (Gambineri et al., 2002). It should be noted that INSL3 levels are associated with LH and ovarian androgenic function in PCOS women, which suggests that INSL3 can be considered as a new circulating hormone associated with LH dependent ovarian hyperandrogenism, particularly, in normal-weight PCOS women.

2. Conclusion

PCOS is presented with adverse hormonal perturbations that raise various gynecological and metabolic changes among the affected women. The pathogenesis of this disease is attributed to genetic factors. Androgen synthesis and consequent circulating levels are augmented as the hallmark feature of PCOS that is linked with the appearance of hirsutism, acne, and alopecia. The primary source of hyperandrogenism in PCOS women is an ovary. The excess androgen production in ovaries is contributed by hyperplasia of thecal cells coupled with the enhanced steroidogenic potential of androgen pathway enzymes. The current study has presented the findings of candidate gene-based association studies of polymorphisms among the genes that are involved in altering androgen levels and steroidogenesis. These actions are meant to govern the phenotypic heterogeneity and susceptibility of this disorder. However, different diagnostic criteria such as the difference in lifestyle, sample size, the contribution of multiple genes, and environmental factors affect the results concluded by the candidate gene studies. DENND1A is identified as the driving force for PCOS hyperandrogenemia. Moreover, an important part is played by alternative splicing of DENND1A to produce a v.2 variant that results in the development of PCOS. A high concentration of DENND1A is observed in theca cells of ovaries. The alteration in

receptor expression contributing to LH hyperstimulation is strengthened on the basis of the relationship between LHCGR locus and PCOS, which enhances steroidogenesis. The role of genetic variants in modulating PCOS hyperandrogenism. However, the genetic underpinnings of a multigenic complex disorder like PCOS can be easily delineated based on the selection of suitable candidate genes. The study results are likely to pave the way towards the establishment of genetic predisposition profiles to design therapeutic management strategies in the coming years.

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