JOURNAL OF COLLEGE OF EDUCATION FOR PURE SCIENCES
Vol. 8, No. 3, September 2018
Website: jceps.utq.edu.iq Email: jceps@eps.utq.edu.iq

Polycystic Ovary Syndrome and related Some Genetic Markers

Enas Abdul Kareem Jabbar
Enaskareemjj0@gmal.com
Department of Biology, College of Science , university of Thi-Qar

Abstract

Polycystic ovary syndrome (PCOS) is the most familiar endocrine disorder affecting women of childbearing could be happen with problem and metabolic anomalies. PCOS women present with ovulatory dysfunction, abnormal hormones, hyperandrogenemia, obesity, and hyperinsulinemia. Patients with PCOS may present complaining of irregular or unpredictable menstrual cycles, undesirable hair growth, acne , scalp hair loss, unexplained weight gain or overweight,and infertility. Clinical phenotyping of PCOS involves determining medical and/or biochemical androgen excess. The bulk of evidence points to the ovary being the source of excess androgens, which appears as a result of an abnormal regulation of steroidogenesis.

It is a heterogeneous disorder which results from interaction of multiple genes and environmental factors.

Key Words : Polycystic ovary syndrome; genetic association; single nucleotide polymorphism; haplotype; pharmacogenetics

متلازمة المبيض المتعدد الكيسات و بعض العلامات الجينية المسببة له

Enas Abdul Kareem Jabbar

Enaskareemjj0@gmal.com

Department of Biology, College of Science , university of Thi-Qar

الخلاصة

تعد متلازمة المبيض المتعدد الكيسات (PCOS) أكثر اضطرابات الغدد الصماء شيوعًا التي تؤثر على النساء في سن الإنجاب ، مما يتسبب ليس فقط في قلة الانجاب او عدمه ولكن أيضًا في التمثيل الغذائي. من الاعراض المظهرية وكذلك السريرية التي تتميز بها نساء متلازمة تكيس المبايض هي ضعف التبويض ، مستوى الهرمونات غير طبيعية ، لكولسترول في الدم ، والسمنة ، وفرط الأنسولين. وتعاني النساء في متلازمة تكيس المبايض من دورات الطمث غير منتظمة أو غير متوقعة ، نمو الشعر غير المرغوب فيه ، حب الشباب أو فقدان شعر فروة الرأس ، زيادة الوزن غير المبررة ، والعقم.

ينطوي النمط الظاهري السريري لـ PCOS على تحديد الزيادة في الأندروجين وكذلك عمل فحص الموجات فوق الصوتية لتحديد المتلازمة وقد اظهرت بعض الدراسات مؤخرا وجود خلل في عدد من الجينات التي اما تكون متعلقة بالتمثيل الغذائي او انتاج الهرمونات وقد تكون المتلازمة ايضا ناتجة عن تفاعل عدد من الجينات مع بعض العوامل البيئية.

Introduction

Polycystic ovary disorder (PCOS) is most widely recognized diseases, confusing endocrine issue and influencing women in their regenerative years. It was described by Stein and Leventhal in 1935. According to the National Institutes of Health (NIH) 1990 criteria, PCOS influences among 6% and 8% of women around the world (Moran *et al*, 2010) it can be noticed among the most widely recognized scatters of humans, and the absolute most basic endocrine anomaly of women of conceptive age.

The etiology of PCOS is obscure, there is expanding confirmation to help a noteworthy hereditary basis, since the disorder is emphatically familial (Legro *et al*., 2002). It is clear that there are multiple genes (and most likely a numerous) add to the heterogeneous phenotype (Urbanek, 2007) the clinical and biochemical introduction is impacted by extra natural elements, for example, eating regimen and exercise (Huber-Buchholz *et al* , 1999).

Nevertheless, by using animal models, and supporting with clinical proof, lead us to suggest that the advancement of PCOS is a direct procedure with a starting point before puberty (the contemporary clinical view of time of beginning of PCOS) based on this formative procedure are cooperating hereditary and external factors that may modify phenotypic expression of PCOS amid grown-up life, especially the powerlessness to an ovulation(Chang *et al*., 2000).

Clinically, infected with PCOS show an expanded hazard for fruitlessness, useless dying, endometrial carcinoma, heftiness, type 2 diabetes mellitus (DM), dyslipidemia, hypertension, and potentially cardiovascular infection (CVD). Moreover, it has imperative familial ramifications . (Azziz, *et al*, 2009).

The genetic basis of the PCOS

ordinary grouping of PCOS has been continually revealed recommending that hereditary components assume a part in the advancement of this disorder, the fact that PCOS cases don't show a reasonable example of Mendelian inheritance (Sheikhh, *et al* , 2007) . currently the recognized that PCOS represents a complex trait like to diabetes mellitus type 2 DM and obesity, and that both hereditary and ecological factors add to the PCOS pathogenesis (Diamanti-Kandarakis and Piperi, 2005).

In general, PCOS can be seen as a heterogeneous androgen overabundance issue with differing level of gonadotropic and metabolic anomalies (Dasgupta and Mohan, 2008). However , there is strong proof for a major hereditary element in the etiology of PCOS. In Families with PCOS cases, there is inheritability of both hyperandrogenaemia and hyperinsulinaemia in influenced kin (Franks and McCarth, 2004).

Various hereditary mechanisms, including autosomal prevailing, changed autosomal prevailing, X-connected overwhelming and multifactorial, have been proposed, in any case, the exact method of legacy of PCOS has not been built up (Franks Gharani and McCarthy, 2001). It has been recommended that numerous loci and epigenetic changes may assume a part in the phenotype. Family history, as a impression of hereditary hazard, can likewise be considered as a hazard factor and, accordingly it s vital for deciding a person's danger of creating PCOS (Menke furthermore, Strauss, 2007).

Heritability of PCOS and Hyperandrogenemia

Family examines show that PCOS is fundamentally more common among relatives than in the all inclusive community (Legro and Strauss, 2002). Among first-degree female relatives 35% of premenopausal moms and 40% of sisters no hormonal treatment were likewise influenced with the disorder, these affection rates are fundamentally higher than the 6-7% saw in the all inclusive community (Azziz *et al*., 2004b).

An extra 24% of sisters had hyperandrogenemia with typical menses. Aggregate and free testosterone levels were comparable between the sisters with hyperandrogenemia just and the sisters with PCOS. A bimodal circulation of testosterone levels in the sisters with PCOS was watched, recommending a noteworthy hereditary segment to hyperandrogenemia (Sam *etal*., 2005).

In their substantial examination, Cooper and partners were the first to portray that the rate of Scarcity of menstruation and Ovarian cysts is extended in first level relatives of PCOS patients contrasted and the controls. Furthermore, in this examination the proposed instrument of legacy was autosomal overwhelming with diminished penetrance (Cooper *et al*., 1968).

Givens and collaborators announced a progression of family-based examinations, utilizing the demonstrative criteria comprising of hirsutism, oligomenorrhea, and extended ovaries. They discovered familial conglomeration of hyperandrogenic and metabolic disarranges (Givens, 1988). These investigations were the first to uncover some of the severe metabolic sequelae, for example, DM, insulin protection, lipid variations from the norm,hypertension, and arteriosclerosis.

Other examination used high-determination ultrasonography to distinguish Ovarian cysts in 61 women with menstrual unsettling influences, hyperandrogenism, weight, furthermore, fruitlessness and additionally in their first-degree female relatives. They establish that 68% of the moms and 87% of the sisters were influenced. In this examination no endeavor was made to distinguish a male phenotype (Hague *et al*., 1988).

In the late seventies, Ferriman and Purdie examined a substantial gathering of women with and without Scarcity of menstruation and their families. They revealed a higher commonness of hirsutism,

oligomenorrhea and fruitlessness in first-degree relatives contrasted and non-hirsute control women. A poll uncovered an expanded hair loss in male relatives. Influenced female and male relatives were not efficiently described in this examination (Ferriman and Purdie, 1979).

In Norwegian investigation, groups of 132 women recognized based on an ovarian wedge resection were contemplated, who additionally had at least two of the next side effects: menstrual anomaly, hirsutism, barrenness, and additionally stoutness. They additional comparison between these women , controls and their families, and they discovered a fundamentally higher level of PCOS-related side effects in the primary level feminine relations of PCOS patients and watched a fundamentally higher level of untimely thinning up top (Lunde *et al*., 1989).

It was accounted for that the rates of PCOS in moms and sisters with PCOS was 24% and 32%, separately (Kahsar-Miller *et al*., 2001).Also, it was seen that 22% of regenerative matured sisters of women with PCOS satisfied the symptomatic criteria of PCOS, while 24% had expanded testosterone and dehydroepiandrosterone sulfate (DHEAS) values with general menstrual cycles (Legro *et al*., 2002). Besides, 16% and 8% PCOScommonness rates in sisters and moms of Turkish PCOS patients, separately were seen (Yildiz *et al*., 2003). Siblings of women with PCOS likewise show strange androgens:an examination of such siblings discovered them to have raised levels of DHEAS (Legro *et al*.,2002). Oligospermia and expanded LH emission were found in a portion of the male subjects of the examination members, recommending a X-connected example of legacy(Givens, 1988). Physiological confirmation that hyperandrogenemia in PCOS is hereditarily controlled is bolstered by the perception that ovarian theca cells expelled from women with PCOS and proliferated in culture show steadily hoisted testosterone discharge contrasted with cells from unaffected women. Since expulsion from the body and increase in culture evacuates the impact of an irregular hormonal milieu from these cells, it is likely that tenacious contrasts from typical speak to natural (hereditary) defects (Nelson *et al*., 1999).

Heritability of Insulin-Related Traits in PCOS

Proof for heritability of metabolic phenotypes, for example, beta cell brokenness and insulin protection was accounted for in family investigations of PCOS, i.e.,PCOS isn't just a heritable condition, yet inside PCOS cases, insulin protection and insulin discharge likewise give off an impression of being under noteworthy hereditary control. The guardians of those with PCOS have expanded predominance of glucose narrow mindedness and sort 2 DM while their siblings and sisters indicate insulin protection contrasted with age-and BMI-coordinated solid controls (Yildiz *et al*., 2003).Additionally, among sisters of women with PCOS, and who had themselves PCOS or hyperandrogenemia with normal

menses; they indicated bring down insulin affectability than unaffected sisters, evaluated by fasting insulin and glucose estimations (Legro *et al*., 2002). In like manner, hyperinsulinemia was found to happen in 69% of all relatives who have relative patients with PCOS, proposing that this characteristic was acquired (Yildiz *et al*., 2003). Moreover, siblings of women with PCOS had insulin protection and endothelial brokenness (Kaushal *et al*., 2004).

In addition, kind of women with PCOS had insulin security and endothelial brokenness (Kaushal *et al*., 2004).Abnormal reactions to insulin in cells that have been expelled from women with PCOS recommend the nearness of natural cell absconds on the grounds that these cells have been expelled from the hormonal milieu show in these women. Lower insulin receptor substrate (IRS)- 1-related phosphatidylinositol 3-kinase (PI3K) movement and higher IRS-2 content were seen in the myocytes of PCOS patients contrasted with controls, despite comparable measures of IRS-1 and the p85 subunit of PI3K (Dunaif *et al*., 2001). In PCOS adipocytes, the most extreme glucose take-up fortified by insulin was found by a few agents (Rosenbaum, Haber and Dunaif, 1993) to be bring down contrasted with controls. the fact that others observed the greatest reaction to be typical (Ciaraldi *et al*., 1992); these last specialists found that the affectability of the reaction to insulin was lacking in PCOS. The measure of glucoseransporter-4 in adipocytes was bring down in PCOS (on either a film protein or cell surface premise) than in controls (Rosenbaum, Haber and Dunaif, 1993). Such absconds are likely caused by anomalous articulation or capacity of genes encoding results of the insulin- signaling pathway.

Candidate genes in PCOS

- **Genes involved in ovarian and adrenal steroidogenesis**

The most widely recognized biochemical variation from the norm in women with PCOS is hyperandrogenemia. Thus, analysts have for been endeavoring to discover alinkage or a relationship amongst PCOS and the genes engaged with the androgen Bio-construction passageway. The most related genes associated with steroidogenesis, are the accompanying:

1- Cytochrome P 450 11 a (CYP11a)

Adrenal and ovarian steroidogenesis begin with the change of cholesterol into progesterone, which is stimulate by the P450 cytochrome side chain splitting chemical encoded by CYP11a situated at 15q24 (Franks *et al*.2000). This change is a rate constraining advance of steroidogenesis. Women with PCOS demonstrated a noteworthy relationship between the alleles of the CYP11a with a 5` untranslated district (UTR) comprising of rehashes of a (tttta)n pentanucleotide, a VNTR (variable number *couple*

rehash) polymorphism and serum testosterone levels , These discoveries are affirmed by free case-control thinks about from Greece (Diamanti-Kandarakis *et al*., 2000) and China (Wang *et al*., 2005). In spite of the fact that these investigations recommended that allelic variations of CYP11a have a part in the etiology of Hyperandrogen production and additionally PCOS, consequent investigations counting one with a substantial example measure from Joined Kingdom and Finland have neglected to locate a noteworthy linkage or relationship between this gene locus as well as its VNTR alleles and PCOS (Tan and Zhu,2005a,b).

2- **Cytochrome P 450 (CYP21)**

The change of 17-hydroxyprogesterone into 11-deoxycortisol which is a stage in adrenal and ovarian steroidogenesis is catalyzed by the 21-hydroxylase chemical encoded by CYP21. The lack of this compound, which is acquired by an autosomal passive characteristic, is in charge of most instances of inherent adrenal hyperplasia, and expanded serum 17-hydroxyprogesterone levels are related with its insufficiency (Azziz *et al*., 1995).Women with utilitarian hyperandrogenism or PCOS have an expanded serum 17-hydroxyprogesterone reaction to ACTH incitement as a typical discovering (Azziz *et al*., 1995). Moreover, patients having both heterozygote CYP21 transformations and clinical side effects show a PCOS-like phenotype (Witchel and Aston, 2000). As needs be, changes of CYP21 have been researched as an applicant gene in patients with PCOS.A few specialists demonstrated that kids with untimely pubarche and youthful young women with hyperandrogenism were heterozygous for changes in CYP21 (Witchel and Aston, 2000). In any case, others found no unmistakable concordance between the CYP21 genotype and the useful root of androgen overabundance (Witchel *et al*., 2005). By and large, CYP21 and related changes appear not to assume a key part in the improvement of PCOS.

3- **Cytochrome P 450 (CYP17)**

Other rate constraining strides of adrenal and ovarian androgen biosynthesis are the transformation of pregnenolone and progesterone into 17-hydroxypregnenolone what's more, 17-hydroxyprogesterone, separately, and in the long run these steroids into dehydro-epiandrosterone and androstenedione, which is catalyzed by the P450c17α catalyst. This catalyst has both 17α-hydroxylase and 17,20-lyase exercises and is encoded by CYP17 situated at 10q24.3 (Sharp *et al*., 2004). It was at first recommended that a misrepresented adrenal and ovarian responsiveness and expanded P450c17α catalyst movement were in charge of upgraded androgen levels in PCOS patients and utilitarian hyperandrogenism (Rosenfield, Barnes and Ehrmann, 1994). Escobar-Morreale what's more,

collaborators likewise proposed that the vast majority of the hyperandrogenic women have expanded P450c17α movement in adrenal and ovarian locales (Escobar-Morreale *et al*., 1997).

As per these investigations, it was accounted for that P450c17α articulation and enzymatic movement expanded in ovarian theca cells from womenwith PCOS and expanded transactivation of the CYP17 promoter , In addition, they detailed out of the blue that CYP17 articulation is Irregular at the plane of mRNA security in PCOS theca cells (Wickenheisser *et al*., 2005).Different examinations, recognized an uncommon T/C single nucleotide polymorphism (SNP) in the promoter area of CYP17 expanding the helplessness to create PCOS (Kahsar-Mill operator *et al*., 2004).

In Marwa *et al* ., 2015 study that discussed the Genotype Distribution of CYP 17 Gene as it found there was a significant distinction ($p<0.05$) between percentage of wild type TT and heterozygote TC. The percentage of TT was significant higher than TC between patients 57.38, 42.62 %, separately. furthermore, there was essentially higher distinction ($p<0.01$) amongst TT and TC in the control gathering (60.00, 40.00) % separately. Likewise, in this study there was a correlation amongst patients and control in TT and TC rate. There was no significant difference between the two gatherings (control and patient) in TT and TC rate. CC genotype was absent in this present investigation. Genotype test was not significantly different amongst cases and controls, but rather just inside each gathering in the present investigation. This outcome fortifies the multifactorial hypothesis of the etiology of this disorder.

4- Cytochrome p 450 (CYP19)

Aromatase is a catalyst complex in charge of a key advance in the biosynthesis of estrogens. This catalyst complex is made out of the cytochrome P450 aromatase and the NADPH cytochrome P450 reductase. It is an individual from the cytochrome P450 superfamily, which are monooxygenases that catalyze numerous responses associated with steroidogenesis. The reactant procedure requires the successive exchange of three sets of electrons, and it expends three moles of lessened NADPH to catalyze a progression of three hydroxylations in the blend of one mole of estrogen (Ghosh *et al*., 2009).Specifically, aromatase is in charge of the aromatization of androgens into estrogens, i.e., it changes over C19 steroids (androgens) to C18 steroids (estrogens). The organic significance of aromatase complex movement is connected not exclusively to its part in the blend of estrogens, yet in addition to its potential impact to be determined of the androgenestrogen proportion in a few tissues (Ghosh *et al*., 2009), P450arom is encoded by CYP19 situated on the long arm of chromosome 15 at position 15p21.1 and 130 kb long. Its 10 exons (the last nine of which are coding) are situated inside 30 kb of each other, and the 93 kb 50- flanking district is thought to have an administrative part (Bulun

et al., 2003). A few single nucleotide polymorphisms (SNPs) of the CYP19 gene were related with variety in serum androgen fixations among women; one of it is the SNP rs2414096. Aromatase insufficiency has been accounted for in a numberof hyperandrogenic patients (Belgorosky and Marco, 2005).

Granulosa cells acquired from medium-sized follicles of PCOS patients have small amount of aromatase movement when contrasted with the control follicles. All PCOS follicles contained low levels of P450arom mRNA, estradiol, and lower aromatase invigorating bioactivity (Jakimiuk *et al*., 1998). These discoveries show that the aromatase movement may be diminished in follicles from PCOS patients , and that the conceivable androgen abundance coming about because of this diminished movement may add to strange follicle advancement. Regardless of whether the CYP19 is a hopeful gene for the pathogenesis of PCOS or of hyperandrogenism has, in this manner, been explored. Linkage and change screening thinks about did not uncover any proof that variety at the CYP19 locus takes an interest in the etiology of PCOS (Söderlund *et al*., 2005). In any case,affiliation thinks about using SNPs and haplotypes indicated relationship with PCOS manifestation score and serum testosterone levels (Petry *et al*., 2005; Petry etal.,2006).

- **Genes involved in steroid hormone effects**

1- Androgen receptor gene

All androgens work through their receptor and this receptor has a place with a group of atomic interpretation factors. The androgen receptor is encoded by a gene (AR) situated at Xq11-12 (Lubahn *et al*., 1988) and is made out of three utilitarian areas: the transactivation space, the DNA restricting space, and the ligand-restricting area. A VNTR polymorphism comprising of CAG rehashes (from 11 to 38 rehashes, a normal of 20) in exon-1, encoding a polyglutamine chain in the Nterminal transactivation area, is implanted in AR (Carson-Jurica, Schrader what's more, O'Malley, 1990). The transcriptional movement of androgen receptor is contrarily associated with the quantity of CAG rehashes. Varieties of these rehashes indeed, even inside the ordinary polymorphic range (11-38 CAGs); have been identified with different scatters related with low-or high-androgenic exercises (Jaaskelainen *et al*., 2005). In this way, diminished number of CAG rehashes with an expanded androgen receptor action could clarify a portion of the PCOS phenotype displaying the typical serum androgen levels and hyperandrogenism side effects (Mifsud, Ramirez and Yong, 2000).Nevertheless, many examinations couldn't discover any relationship between this VNTR and PCOS (Urbanek *et al*., 1999; Mifsud, Ramirez and Yong,2000; Jääskeläinen *et al*., 2005). Despite what might be expected, others showed an essentially more prominent recurrence of alleles with longer CAG rehashes (> 22

rehashes) for barren PCOS patients contrasted and rich women (Hickey, Chandy and Norman, 2002). Accordingly, no persuading proof exists about the part of AR in the pathogenesis of PCOS.

2- Sex hormone-binding globulin gene (SHBG)

Human SHBG is made out of a homodimeric glycoprotein created by hepatocytes and is encoded by a 4-kb gene at the 17p12-p13 SHBG manages the entrance of androgens to target tissues. Serum SHBG levels are generally low in patients with hyperandrogenism, particularly in relationship with PCOS, which adds to expanded tissue androgen accessibility (Pugeat *et al.*, 1996). A pentanucleotide rehash polymorphism, (TAAAA)n has additionally been exhibited to impact the transcriptional movement of SHBG gene, that could add to singular assorted varieties in plasma SHBG levels and accordingly impact the entrance of androgens to target tissues(Berube *et al.*,1990).

This polymorphism of the SHBG gene has been observed to be related with PCOS (Xita *et al.*, 2003; Cousin *et al.*, 2004). On the invert others could not discover any affiliation or linkage between a marker near the SHBG locus also, PCOS (Urbanek *et al.*, 1999; Ferk, Teran and Gersak, 2007).

❖ **Genes involved in gonadotropin action and regulation**

1- LH and its receptor genes

Both expanded LH levels and changed LH activity are habitually seen in PCOS patients, and these variations from the norm are related with anovulation through, at any rate to some degree, an unfavorable impact of LH on oocyte development (Balen, 1993). Along these lines, the gene encoding the β-subunit of LH, in charge of LH specificity, has been investigated in PCOS patients. Rajkhowa and partners investigated the ramifications of the basic hereditary variation (V) of the human luteinizing hormone (LH) β-subunit gene (v-LH) in both groups and found that the event of these changes in LH β-subunit gene was not elevated in PCOS contrasted and sound women (Rajkhowa *et al.*, 1995). Then again, subgroup examination of thisstudy uncovered that fat PCOS patients had a higher recurrence of the heterozygous v-LH contrasted and the hefty controls (Elter *et al.*, 1999). It was theorized that change in the LH receptor gene may be a reason for hyperandrogenism in PCOS having ordinary serum LH fixations and raised androgen levels. All things considered, in a resulting preparatory consider, those creators did not discover any transformations after gene sequencing in these influenced families (Franks, Gharani and McCarthy, 2001).

2- **Follistatin gene**

Follistatin, a monomeric glycoprotein encoded by a solitary gene, is fundamentally random to the TGF-β superfamily, yet is connected practically through its part as a high-liking restricting protein for activin. This last is a dimeric glycoprotein having a place with the TGF-β superfamily, prompts FSH

and insulin emission, ovarian follicular development and represses LH-invigorated ovarian androgen creation. As an activin-restricting protein, follistatin can invert each of these activin-incited reactions in vitro and in vivo (Knight and Glister, 2001). Intemperate activin balance because of expanded follistatin may,thusly, decrease FSH fixations, capture follicular development, increment androgen creation, and disable insulin discharge. Since these progressions are ordinary highlights of PCOS (Legro *et al*., 1998b), follistatin gene has beeninvestigated as a competitor gene in PCOS.It was accounted for that there was factually critical linkage between the follistatin gene and PCOS (Urbanek *et al*., 1999). Notwithstanding, consequent more complete follistatin gene examinations directed by similar creators have not acquired any noteworthy linkage (Urbanek *et al*., 2000). Similarly, no noteworthy change in coding areas of the follistatin gene was found by another gathering of specialists (Calvo *et al*., 2001).

In enas ., 2018 study that detected about the single nucleotide polymorphism SNP by sequencing in exon 6 of follistatin gene this study has been found there are eight SNP in that exon but these SNP constitute a non-synonym mutation.

❖ **Genes involved in insulin action and secretion**

Nearly for two decades back, it was shown that most PCOS patients either large or non-corpulent, contrasted and typical women, showed variable degrees of insulin protection and compensatory hyperinsulinemia. Along these lines persuading proof has been begun to gather, and at show, it is outstanding that hyperinsulinemia and insulin protection are basic highlights of PCOS patients (Yildiz *et al*., 2003). Accordingly, various genes associated with insulin activity and emission have been investigated as competitor genes in PCOS pathogenesis, i.e., the insulin gene (INS), the insulin receptor gene (INSR), the insulin receptor substrate genes (IRSs) and calpain-10 gene (CAPN10) (Wiltgen *et al*., 2007).

1- The insulin gene (INS)

The INS is situated between the genes for tyrosine hydroxylase and IGF-II at 11p15.5, and incorporates variable pair rehashes (VNTR) implanted at the 5- administrative locale of INS (Junien and van Heyningen, 1990). The VNTR polymorphism directs the transcriptional rate of the INS and presumably that of the gene encoding IGF-II. The quantity of the rehashes of the INS VNTR ranges from 26 to 200, and because of this element INS VNTR polymorphism has three size classes (Pugliese and Miceli, 2002).Class-I alleles make the shorter polymorphic district, comprising of an normal length of 40 rehashes. Class-II alleles have a normal length of 80 rehash units and are unprecedented in Caucasian. Class-III alleles form the longest polymorphic locale having a normal of 157 rehashes.

Transcriptional action of the more drawn out polymorphic district is more noteworthy than that of the shorter one. Other than their impact on directing INS articulation, they have been involved in the pathogenesis of sort 2 DM in many examinations (Ong *et al*., 1999). It isn't known whether the hyperinsulinemia recognized in PCOS is an result of essential insulin protection or the immediate impact of pancreatic β-celldisorder, while surrenders in both insulin activity and in pancreatic β-cell work have been accounted for (Holte *et al*., 1995).Clear relationship amongst PCOS and allelic variety at the INS VNTR locus was discovered (Michelmore *et al*., 2001). Be that as it may, in more far reaching considers, no confirmations for the linkage of INS and PCOS and for the relationship of the class III allele and of hyperandrogenemia was watched (Calvo *et al*., 2002; Ioannidis *et al*., 2003; Powell *et al*., 2005).

It was found in another research There was numerous fluctuation in insulin gene (INS-promoter). The study have recognized by sequencing (73) mutation in (21) women of the aggregate (50) women with PCOS went around (42%). While the level of hereditary transformations in women who experience the insulin resistance (PCOS group) around 64% (16 patients of the aggregate 50). The percentage of mutations in the healthy gathering for the most part extends (40%).

The rates of mutation in diabetes (INS-promoter) might be diverse due to harm in different genes influence crafted by the insulin gene. Allelic variety at VNTRs (promoter area) may assume an imperative general part in human disease The impact of change on insulin gene (INS-promoter) was represented to by affecting on control of insulin secrtion and activity. In Mohammad *et al* ., 2015 study demonstrated that there was (50.68%) missense prompting the effect on phenotype that prompt Substitution in amino acids (Progress = 31.91% and Transversion = 68.08%) in PCOS group. The deletion and insertion mutations prompts frame shift there was around (30.13%) in this research. These mutations brought about a totally unique translation (defect protein) . A silent mutation which code for a similar amino acid and change in the DNA sequence . Where consequences of this research demonstrated that the percentage of Silent mutations (19.17%).

2- Insulin receptor (INSR)

The insulin receptor is a heterotetrameric glycoprotein, it is an individual from tyrosine kinase receptor family, comprises of two α and β dimmers that are connected by disulfide bonds. It is realized that α subunit contains a ligand-restricting area what's more, the β subunit has a related tyrosine kinase movement. It is encoded by the INSR situated at the chromosome 19p13.2, made out of 22 exons and ranges more noteworthy than 120 kilobase sets (kbp) (Talbot *et al*., 1996). The locale of exons 17-21

encodes the tyrosine kinase space of the receptor, which is important for insulin flag transduction. Change in these exons has been appeared to cause extreme insulin protection and hyperinsulinemia (Krook *et al*., 1994). Official of an insulin atom initiates the kinase action of the receptor, and autophosphorylation of particular tyrosine deposits happens (Li *et al*., 2002).A few sorts of polymorphisms have been recognized inside the coding also, noncoding districts of INSR in patients with PCOS. Of these polymorphisms, most were quiet single-nucleotide polymorphisms (SNPs) and there was a higher recurrence of SNP in exon 17 of INSR (Siegel *et al*., 2002). It was expressed that the number and fondness of insulin receptor isn't changed in PCOS however its tyrosine phosphorylation status and ensuing flagging is influenced, recommending the imperfection may lie in the β-chain (Diamanti-Kandarakis and Papavassiliou, 2006). Among the SNPs in exon 17 of INSR identified to date (Krook *et al*., 1994; Talbot *et al*., 1996; Siegel *et al*., 2002), the C/T SNP at His1058 in the tyrosine kinase area containing the adenosine triphosphate ATP restricting site of INSR has been appeared to be altogether connected with the improvement of PCOS most conceivably by the resultant impacts on the autophosphorylation of the INSR work in a few women with PCOS (Siegel *et al*., 2002; Diamanti-Kandarakis and Papavassiliou, 2006). Be that as it may, these past examinations had not researched the connection between the INSR exon 17 polymorphism and the insulin protection in the women with PCOS, nor had the connection between the INSR exon 17 polymorphism and the INSR β-subunit articulation in the women withPCOS.A few investigations were directed to distinguish whether the transformations of INSR could clarify insulin protection in women with PCOS. At first, coordinate sequencing of INSR from two corpulent women with PCOS did not uncover any changes (Sorbara *et al*., 1994). This finding was bolstered by crafted by two gatherings; right off the bat Conway and colleagues broke down the succession of the tyrosine kinase space of INSR in 22 hyperinsulinemic patients with PCOS. Besides; Talbot and partners explored the transformations by atomic checking of the whole coding district of INSR in 24 hyperinsulinemic women with PCOS. None of these gatherings distinguished huge transformations identified with insulin protection in PCOS (Conway, Avey and Rumsby, 1994; Talbot *et al*., 1996).In inconsistency, a third gathering demonstrated the relationship with INSR in women with PCOS (Tucci *et al*., 2001). However, this affiliation couldn't be affirmed in a back to back investigation from the Mediterranean region (Villuendas *et al*.,2003). In more far reaching study, Urbanek and associates showed a linkage with PCOS in a gathering of very much portrayed 367 families including people prevalently of European starting point with PCOS (Urbanek *et al*., 2005).

In a study conducted Screening for Single Nucleotide Polymorphism in Insulin Receptor Gene in Iraqi Women with PCOS *No SNP polymorphism found* , In the PCR-RFLP investigation of the exon 17 of the INSR polymorphism, all the tried examples from both PCOS and control bunches uncovered no polymorphisms on the grounds that no Pml I acknowledgment site was evident for the increased PCR piece all examples uncovering a band of 317 bp after restriction.

While another study found the genotyping dispersions of exon 17 of INSR genes; the CC, CT and TT genotypes were essentially different in PCOS patients from that of the control women (p=0.002). Additionally, the genotypes of the hefty PCOS patients were likewise not the same as that of the fat control women (p=0.034). No significant difference in the conveyance of these genotypes was seen between non-fat PCOS patients and non-hefty control women (p=0.056). On the opposing, no critical contrast was found between the fat and non- obese PCOS patients (p=0.325). Concerning the allelic recurrence of exon 17 of INSR gene, PCOS patients displayed high recurrence of CC and low recurrence of TT genotypes (p=0.001; p=0.013, separately) yet not with CT genotype of the exon 17 of INSR gene when contrasted with the control women. (Manal *et al* ., 2014) .

3- Insulin receptor substrate proteins

Start of the insulin receptor following insulin limiting requires the autophosphorylation of the β-subunit of the insulin receptor (Hubbard *et al*., 1994). The subsequent tyrosine kinase activity delivered after autophosphorylation will phosphorylate insulin receptor substrates (IRS, for example, IRS-1 and IRS-2 (Dunaif, 1997). A brief span later, IRS-1 and IRS-2 tie and start downstream effectors, for instance, hosphoinositide 3-kinase, to propel the metabolic and mitogenic exercises of insulin. Exactly when IRS-1 is broken, IRS-2 is the essential emissary for the intracellular transmission of the insulin signal, yet it requires a higher insulin obsession for start(White, 2002).

A few polymorphisms of IRS1 and IRS2 genes have been ensnared in insulin protection. The Gly972Arg polymorphism for IRS-1 and Gly1057Asp for IRS-2 have been appeared to build helplessness to type 2 DM (Burks and White, 2001; Jellema *et al*., 2003). Albeit at first no proof for linkage or relationship with PCOS was found with IRS-1 (Urbanek *et al*., 1999). Sir- Petermann and partners detailed a higher recurrence of the Arg972 IRS-1 allele in PCOS patients in Chilean populace (Sir-Petermann *et al*., 2001).

In opposite, different investigations couldn't discover any distinctions in the conveyance of IRS-1 Gly972Arg and IRS-2 Gly1057Asp alleles in PCOS patients and controls; in any case, they exhibited that the Gly972Arg IRS-1 was more pervasive in insulin-safe patients contrasted and the non-insulin

safe patients or control subjects (El Mkadem *et al*., 2001; Ehrmann *et al*., 2002a; Villuendas *et al*., 2005).

4- Calpain-10 gene

Calpain-10 is a cysteine protease that assumes a part in insulin emission and activity (Sreenan *et al*., 2001), and hereditary examinations have demonstrated that variety in the gene (CAPN10) encoding calpain-10 is related with type 2 DM (Horikawa *et al*., 2000).

Because of the way that PCOS and sort 2 DM share various etiologic factors (Ehrmann, 1997), Ehrmann and partners in 2002 tried to decide regardless of whether variety in the CAPN10 is related with quantitative characteristics identified with the pathogenesis of PCOS and sort 2 DM. They found a relationship between this gene and higher insulin levels in African-American women and an expanded danger of PCOS in both African-American and white women (Ehrmann *et al*., 2002b).

Gonzales and associates explored whether four SNPs (SNP-19, SNP- 43, SNP-44, and SNP 63) of the CAPN10 were related with PCOS. In support of the last mentioned, they announced in their continuous examinations that SNP-44 of the gene is related with PCOS (Gonzalez *et al*., 2002; Gonzalez *et al*., 2003). Nevertheless , different examinations couldn't affirm any relationship with PCOS in a more thorough examination (Escobar-Morreale *et al*., 2002; Haddad *et al*., 2002).

In an Iraqi study delt the polymorphism in UCSNP43,44 to ixon 3 of Calpain-10 gene of Polycystic Ovary Syndrome women in Thi Qar Proviance this study investigated the association between the Caplain-10 gene haplotype UCSNP-43, 44 and PCOS for the first time in Iraqi population; however, there is a little number of reports on the role of calpain 10 in the pathogenesis of PCOS. though, we need to discuss which alleles or haplotypes carry the risk of developing PCOS. In the current study, we sequenced two regions (SNPs-43,44) to discover the association between calpain 10 and PCOS. Our results showed that the values of ORs from haplotypes frequencies confirm the protective association between SNPs-43 and PCOS (OR=0.26. p= 0.32) we revealed a high association (increase risk) between SNPs-44 and PCOS in some cases (OR=3.86, p=0.32)(Enas *et al* ., 2017).

❖ **Genes associated with vitality homeostasis**

1- The genes of leptin, leptin receptor, and adiponectin

In spite of the fact that the fat tissue has for some time been viewed as a latent and latent kind of connective tissue that stores and discharges vitality, amid the last decade it has been perceived that it isn't just a connective tissue but on the other hand isone of the dynamic endocrine organs which secretes a wide assortment of items called as adipocytokines (Kershaw and Flier, 2004).

Because of the way that a generous extent of women with PCOS are overweight, many are corpulent and some are to a great degree stout, the genes of the most well known adipocytokines, for example, leptin and adiponectin have been researched as applicant genes in the pathogenesis of PCOSThe agents sequenced the leptin gene in PCOS patients, yet they neglected to recognize any transformations of the coding exons. They additionally sequenced the leptin receptor gene and discovered already distinguished amino corrosive variations in exons 2, 4, and 12 and in addition the pentanucleotide inclusion in the 3-untranslated locale. Be that as it may, the allele frequencies of these polymorphisms did not contrast from those in the all inclusive community (Oksanen *et al*., 2000).

After the grouping polymorphisms of adiponectin gene distinguished in people, most investigations have concentrated on two polymorphisms, T45G in exon 2 and G276T in intron 2. It was shown reliably that these polymorphisms connect with heftiness, insulin protection, and the danger of sort 2 DM (Hara *et al*.,2002; Menzaghi *et al*., 2002; Stumvoll *et al*., 2002; Hu *et al*., 2004). Others neglected to discover any relationship amongst PCOS and these two normal polymorphisms of the adiponectin gene (San Mill'an *et al*., 2004).

All the more as of late, two unique investigations from Greece and Spain countered the likelihood that the T45G and G276T polymorphisms of adiponectin gene could be related with PCOS. Furthermore, these investigations detailed the clashing comes about impacts of these SNPs on adiponectin and hormonal factors (Xita *et al*., 2005; Escobar-Morreale *et al*., 2006).

Taken together, these information propose that unique in relation to the next insulin safe issue; the adiponectin gene appears not to assume a causative part in the pathogenesis of PCOS.

2- **Peroxisome proliferator-activated receptor-γ gene**

Peroxisome proliferator-initiated receptor-γ gene (PPAR-γ) is a interpretation calculate included adipogenesis, vitality digestion and a utilitarian receptor for thiazolidinediones (TZDs) presented as insulinsensitizing operators (Rangwala and Lazar, 2004). Also, PPAR-γ gene (PPAR-γ) situated on 3p25 (Elbrecht *et al*., 1996) is a hopeful gene for the direction of fat tissue digestion in people and furthermore a weakness gene for the advancement of both corpulence and DM (Altshuler *et al*., 2000).Since PCOS and sort 2 DM share certain phenotypic highlights, for example, weight and insulin protection, a few examinations researched the potential helpful impacts of TZDs on the ovulatory brokenness, hirsutism, hyperandrogenism and insulin-protection of PCOS (Ghazeeri *et al*., 2003).

Two PPAR-γ gene polymorphisms have been completely explored in different populaces (Meirhaeghe and Amouyel, 2004). Some saw no confirm for any linkage or relationship with PCOS for a marker near the PPAR-γ gene (Urbanek *et al*., 1999). Others announced that the Pro12Ala polymorphism of

PPAR-γ are related with expanded insulin affectability as well as lower hirsutism scores in PCOS women (Hahn *et al*., 2005). Be that as it may, this sort of polymorphism was not observed to be related with PCOS in women from Spain (San Millán *et al*., 2004), Italy (Orio *et al*., 2003) and China (Wang *et al*., 2006).

Even though genetic association studies do not clearly establish any link between PCOS and PPAR-γ polymorphisms, functional investigations still point out the suspicious role of PPAR-γ on PCOS.

❖ **Genes involved in chronic inflammation**

Chronic inflammation seems to assume a part in the improvement of insulin protection and CVD (Fern'andez-Genuine and Ricart, 2003) and it may be associated with the pathogenesis of PCOS (Diamanti-Kandarakis *et al*., 2006) .

despite the fact that not all concur (Möhlig *et al*., 2004). Some genomic variations identified with irritation have been examined in PCOS.

1- Tumor necrosis factor (TNF-α)

Tumor **necrosis** factor (TNF)- α is cytokine discharged by fat tissue that assumes a critical part in insulin protection (Hotamisligil *et al*., 1996). The polymorphisms in the TNF-α gene don't appear to have a key part in the pathogenesis of PCOS (Escobar-Morreale *et al*., 2001; Korhonen *et al*., 2002).Different genes engaged with interminable aggravation, for example, TNFR2 (type-2 TNF receptor) gene (Peral *et al*., 2002), Interleukin - 6 (IL-6) (Möhlig *et al*., 2004), IL-6 flag transducer gp 130 and IL-6 receptor (Escobar-Morreale *et al*., 2003) genes have additionally been examined as a competitor gene for pathogenesis of PCOS, in another study that dealt Tumor Necrosis Factor-` (-308 G/A) Gene Polymorphism in Iraqi women that the genotype dissemination happens both in patients and control furthermore, as per allelic conveyance as, homozygous (either AA or GG allele found), and heterozygous mutation (nearness of AG alleles). It has been discovered that there is no noteworthy distinction of TNF-a quality in PCOS patients contrasted and control gathering . The relationship of hereditary mutation of TNF-a - 308 G/A allele polymorphism with age, BMI and other biochemical parameters in patients and control gatherings. TNF-a gene was arranged by allelic dispersion into homozygous, heterozygous, or nonappearance of mutation alleles. The age variable has been subdivided into age interim gatherings (<25 years, 25– 34 years, 35– 45 year) when related with TNF-an (allele A,G) in the two patients and control gatherings and measurably utilizing Chi square test (Fadhil *et al* ., 2017).

CONCLUSIONS

In this review that described summary of the current state of genetic studies of PCOS which is reveled that there are many genes contributed to pathogen of PCOS and these study needs more confirmation , samples and technique , Within the past few years, new reagents and tools have been assembled to make successful analysis of genetically complex disorders eminently feasible: these tools include a nearly complete catalogue of common human genetic variation by the International HapMap Project efficient and relatively inexpensive high-volume genotyping technologies, development of easily accessible analysis software, and, most important, the assembly of sufficiently large PCOS patient cohorts to detect genetic variants with effect sizes as observed in other complex diseases. When applied to candidate genes, these tools make it possible to fully explore the genetic relevance of these genes to the etiology of PCOS and may help to reconcile some of the discrepant results observed in studies of different variants within the same gene. Finally, it is now possible to carry out genome-wide association studies of PCOS that will identify potentially novel and unexpected genes and variants contributing to the etiology of PCOS. The next 10 years promise to be a very exciting and productive era in the genetic analysis of PCOS.

Refrences

Azziz R, Carmina E and Dewailly D. (2009) The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril*, 91:456–88.

Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. (2004b) The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*, 89:2745–9.

Belgorosky A, Pepe C, Marino R, Guercio G, Saraco N, Vaiani E, Rivarola MA. (2003) Hypothalamic-pituitary-ovarian axis during infancy, early and late prepuberty in an aromatase-deficient girl who is a compound heterocygote for two new point mutations of the CYP19 gene. *J Clin Endocrinol Metab*, 88(11):5127-31.

Bulun SE, Sebastian S, Takayama K, Suzuki T, Sasano H and Shozu M. (2003) The human CYP19 (aromatase P450) gene: update on physiologic roles and genomic organization of promoters. *J Steroid Biochem Mol Biol*,86:219–24.

Chang PL, Lindheim SR, Lowre C, Ferin M, Gonzalez F, Berglund L, Carmina E, Sauer MV & Lobo RA. (2000) Normal ovulatory women with polycystic ovaries have hyperandrogenic pituitary–ovarian responses to gonadotropinreleasing hormone-agonist testing. *J Clin Endocrinol Metab*,85: 995–1000.

Ciaraldi TP, el-Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SS. (1992) Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. *J Clin Endocrinol Metab*,75:577–83.

Cooper HE, Spellacy WN, Prem KA and Cohen WD. (1968) Hereditary factors in the Stein-Leventhal syndrome," *Am J Obstet Gynecol*, 100 (3): 371–87.

Dasgupta S, Mohan Reddy B. (2008) Present status of understanding on the genetic etiology of polycystic ovary syndrome. *J Postgrad Med*,54:115-25.

Diamanti-Kandarakis E, Piperi C. (2005) Genetics of polycystic ovary syndrome: searching for the way out of the labyrinth. *Hum Reprod Update*, 11: 631-43.

Dunaif A, Wu X, Lee A, Diamanti-Kandarakis E. (2001) Defects in insulin receptor signaling in vivo in the polycystic ovary syndrome (PCOS). *Am J Physiol Endocrinol Metab*, 281:392–9.

Enas Abdul Kareem Jabbar, Alia E Mahmood, Majida G. Magtooph, and mohammed Hashim : (2017) ; Study the polymorphism in UCSNP43,44 to ixon 3 of Calpain-10 gene of Polycystic Ovary Syndrome women in Thi Qar Proviance ; J.Thi-Qar Sci,Vol.6(2) p: 50-58.

Enas Abd-Alkareem Jabaar ., 2018 ; Single Nucleotide Polymorphism SNP Analysis of Exon6Follistatin Gene Relatedtopolycystic Ovarian Syndrome inThiQar Governorate ; Journal of University of Babylon, Pure and Applied Sciences, Vol.(26), No.(4): 2018 ; pp : 293-307

Escobar-Morreale HF, Serrano-Gotarredona J, Garc´ıa- Robles R, Sancho JM and Varela C. (1997) Lack of an ovarian function influence on the increased adrenal androgen secretion present in women with functional ovarian hyperandrogenism. *Fertil Steril*, 67(4):654–62.

Fadhil Jawad Al-Tu'ma,, Noor Hadi Ferhan,and Wasan Ghazi Al-Saf : (2017) ; Polymorphism of tumor necrosis factor-alpha 308 G/A gene in Iraqi patients with polycystic ovarian syndrome : *Iraq Med J* | Vol. 1, No. 2, Spring 2017: 48–52.

Ferriman D and Purdie A W. (1979) The inheritance of polycystic ovarian disease and a possible relationship to premature balding. *Clin Endocrinol*, 11(3): 291–300.

Franks S and McCarthy M. (2004) Genetic of ovarian disorders: Polycystic ovary syndrome. *Rev Endo Metab Disord*, 5:69-76.

Franks S, Gharani N and McCarthy M. (2001) Candidate genes in polycystic ovary syndrome. *Hum Reprod Update*, 7:405-10.

Ghosh D, Griswold J, Erman M, Pangborn W. (2009) Structural basis for androgen specificity and oestrogen synthesis in human aromatase. *Nature*, 457 (7226): 219–23.

Givens JR. (1988) Familial polycystic ovarian disease. *Endocrinol Metab Clin Nor Am*, 17(4): 771–83.

Hague W M, Adams J, Reeders ST, Peto TEA and Jacobs HS. (1988) Familial polycystic ovaries: a genetic disease?. *Clin Endocrinol*, 29(6): 593–605.

Huber-Buchholz MM, Carey DG & Norman RJ. (1999) Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab, 84: 1470–4.

Jakimiuk J, Weitsman SR, Brzechffa PR and Magoffin DA. (1998) Aromatase mRNA expression in individual follicles from polycystic ovaries. Mol *Hum Reprod*, 4(1): 1–8.

Kahsar-Miller M, Boots LR, Bartolucci A and Azziz R. (2004) Role of a CYP17 polymorphism in the regulation of circulating dehydroepiandrosterone sulfate levels in women with polycystic ovary syndrome. *Fertil Steril*, 82(4): 973–5.

Kahsar-Miller M, Nixon C, Boots LR, Go RCP, Azziz R. (2001) Prevalence of the polycystic ovary syndrome (PCOS) among first degree relatives of patients with PCOS. *Fertil Steril*, 75:53–8.

Kaushal R, Parchure N, Bano G, Kaski JC, Nussey SS. (2004) Insulin resistance and endothelial dysfunction in the brothers of Indian subcontinent Asian women with polycystic ovaries. *Clin Endocrinol (Oxf)*, 60:322–8.

Legro RS and Strauss JF. (2002) Molecular progress in infertility: polycystic ovary syndrome. *Fertil Steril*, 78:569-76.

Legro RS and Strauss JF. (2002) Molecular progress in infertility: polycystic ovary syndrome. *Fertil Steril*, 78:569-76.

Lunde O, Magnus P, Sandvik L and Hoglo S. (1989) Familial clustering in the polycystic ovarian syndrome. *Gynecol Obstet Invest*, 28(1): 23–30.

Manal T. Mutib., Farqad B. Hamdan., Anam R. Al-Salihi : (2015): INSR gene variation is associated with decreased insulin sensitivity in Iraqi women with PCOs : *Iran J Reprod Med Vol. 12. No. 7. pp: 499-506, July 2014* Original article

Marwa B. Mohammed, Salwa J. AL-Awadi, Mahfoodha A. Omran : (2015); Association Between Polycystic Ovary Syndrome and Genetic Polymorphisms of CYP 17 Gene in Iraqi Women ; Iraqi Journal of Biotechnology, 2015, Vol. 14, No. 2 , 99-110.

Maysaa Abdul Razzaq Dhahi : (2013) : Molecular Screening for Single Nucleotide Polymorphism in Insulin Receptor Gene in Iraqi Women with Polycystic Ovarian Syndrome : International Journal of Modern Biology and Medicine, 2013, 3(1): 17-26

Menke MN, Strauss JF. (2007) Genetic approaches to polycystic ovarian syndrome. Curr Opin Obstet Gynecol, 19:355-9.

Mohammad Ibraheem Mezaal*, Mohammed Ibrahim Nader, Ismail Hussein Aziz : (2015) : Molecular Study of Insulin Resistance and Polycystic Ovary Syndrome: American Journal of Medicine and Medical Sciences Vol. 5(3): 121-125 DOI: 10.5923/j.ajmms.20150503.02

Moran C, Tena G, Moran S, Ruiz P, Reyna R & Duque X. (2010) Prevalence of polycystic ovary syndrome and related disorders in Mexican women. Gynecol Obstet Invest, 69(4): 274-80.

Nelson VL, Legro RS, Strauss JF, McAllister JM. (1999) Augmented Androgen Production Is a Stable Steroidogenic Phenotype of Propagated Theca Cells from Polycystic Ovaries. *Mol Endocrinol*, 13:946-57.

Petry CJ, Ong KK, Michelmore KF, Artigas S, Wingate DL, Balen AH, de Zegher F, Ibáñez L, Dunger DB. (2006) Associations between common variation in the aromatase gene promoter region and testosterone concentrations in two young female populations. *J Steroid Biochem Mol Biol*, 98(4-5): 199–206.

Petry CJ, Ong KK, Michelmore KF, Artigas S, Wingate DL, Balen AH, de Zegher F, Ibáñez L, Dunger DB. (2005) Association of aromatase (CYP 19) gene variation with features of hyperandrogenism in two populations of young women. *Hum Reprod*, 20(7):1837-43.

Rosenbaum D, Haber RS, Dunaif A. (1993) Insulin resistance in polycystic ovary syndrome: decreased expression of GLUT- 4 glucose transporters in adipocytes. *Am J Physiol*, 264:197–202.

Rosenfield RL, Barnes RB and Ehrmann DA. (1994) Studies of the nature of 17- hydroxyprogesterone hyperresponsiveness to gonadotropin-releasing hormone agonist challenge in functional ovarian hyperandrogenism. *J Clin Endocrinol Metab*, 79(6):1686–92.

Sam S, Legro RS, Bentley-Lewis R, Dunaif A. (2005) Dyslipidemia and metabolic syndrome in the sisters of women with polycystic ovary syndrome.*J Clin Endocrinol Metab*, 90: 4797–802.

Sharp L, Cardy AH, Cotton SC and Little J. (2004) CYP17 gene polymorphisms: prevalence and associations with hormone levels and related factors. A HuGE review. *Am J Epidemiol*, 160(8):729–40.

Sheikhh MH, Kalantar SM, Ghasemi N. (2007) Genetics of polycystic ovary syndrome. *Iran J Reprod Med*, 5(1):1-5.

Söderlund D, Canto P, Carranza-Lira S, Méndez JP. (2005) No evidence of mutations in the P450 aromatase gene in patients with polycystic ovary syndrome. *Hum Reprod*, 20(4): 965–9.

Tan L and Zhu G. (2005a) Relationship between the microsatellite polymorphism of CYP11α gene and the pathogenesis of hyperandrogenism of polycystic ovary syndrome in Chinese. *Chinese J Med Genet*, 22(2): 216– 8.

Tan L and Zhu G. (2005b) Role of the pentanucleotide (tttta)n polymorphisms of Cyp11alpha gene in the pathogenesis of hyperandrogenism in Chinese women with polycystic ovary syndrome. Journal of Huazhong University of Science and Technology. *Med Sci*, 25(2): 212–4.

Urbanek M. (2007) The genetics of the polycystic ovary syndrome. *Endocrinol Metab*, 3 (2): 103-11.

Wang Y, Wu XK, Cao YX, Yi L, Zou Y, Qu JW, Hou LH. (2005) Microsatellite polymorphism of (tttta)n in the promoter of CYP11a gene in Chinese women with polycystic ovary syndrome. *Zhonghua Yi Xue Za Zhi*, 85(48):3396–400.

Wickenheisser JK, Nelson-DeGrave VL and McAllister JM. (2005) Dysregulation of cytochrome P450 17α-hydroxylase messenger ribonucleic acid stability in theca cells isolated from women with polycystic ovary syndrome. *J Clin Endocrinol Metab*, 90(3): 1720–7.

Witchel SF and Aston C E. (2000) The role of heterozygosity for CYP21 in the polycystic ovary syndrome. *J Pediatr Endocrinol Metab*,13(suppl 5):1315–7.

Witchel SF, Kahsar-Miller M, Aston CE, White C, and Azziz R. (2005) Prevalence of CYP21 mutations and IRS1 variant among women with polycystic ovary syndrome and adrenal androgen excess. *Fertil Steril*, 83(2):371–5.

Yildiz BO, Yarali H, Oguz H, Bayraktar M. (2003) Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. *J Clin Endocrinol Metab*, 88:2031–6.