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ORIGINAL ARTICLE

Distribution Of FSHR, ESR1 And ESR2 Snps Among Women With Polycystic Ovary Syndrome Undergoing In Vitro Fertilization

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ABSTRACT
Polycystic Ovarian Syndrome is the most common endocrine and a complex heterogeneous disorder of women in their reproductive age. The aim of this study was to determine whether polymorphism in FSHR, ESR1 and ESR2 were associated with clinical features of PCOS patient in Iranian population. Polycystic ovary syndrome (PCOS) patients (n=100) and controls (n=100) that referred to department for in vitro fertilization because of tubal and/or male infertility undergoing in vitro fertilization (IVF) were studied. DNA extraction and digestion by PCR- restriction fragment length polymorphism were used to detect the polymorphic genotypes. Chi-square test and the frequency differences of alleles and genotypes between two groups were compared. A conventional p-value of ≤ 0.05 was considered significant. The results suggest that GA genotype of Ala307Thr, Ser680Asn of FSHR appear more frequent in PCOS patients and might play a role in genetic susceptibility to PCOS (P=0.001). In contrast no significant difference was found in genotypic distribution of ESR1 (P=0.871) and ESR2 (P=0.336) between cases and control groups.Results indicate that a statistically significant association between genotype of two polymorphism of FSHR with PCOS. PCOS patients carry more often the GA genotype at positions 307 and 680 variant. Also According to the Chi-square test results, the differences were not significant for SNPs. of ESR1 and ESR2.
Keywords: *Follicle stimulating hormone receptor, estrogen receptor, polymorphism, polycystic ovary syndrome*

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Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women, characterized by hyperandrogenism, insulin resistance, obesity and accounts for more than 75% of cases of anovulatory infertility, affecting about 4-8% of women of reproductive age globally [1,2,3].

Recently the number of genes involved in susceptibility to PCOS increased dramatically, each with individually effect which interacts with one another. In the search for genes involved in the etiology of PCOS, the focus has been on candidate genes FSHR, ESR1 and ESR2 [6,7,8,9].

Follicle stimulating hormone receptor gene that is located both in sertoli cells of the testis and granolusa cells of the ovaries is the most studied genetic factor in women with Polycystic Ovarian Syndrome (11).

FSHR gene is situated on chromosome 2p21 and comprises 10 exons. Most studies focused on tow SNPs { Thr307Ala (rs6165), Asn680Ser (rs6166)} that located on exon 10 and are in near complete linkage disequilibrium, one located in the extracellular domain at position 307and the other one located in the intracellular domain at position 680.

There is a number of genetic variant of FSHR that have an effect on the phenotype, These effects include variable development of secondary sex characteristics, primary amenorrhea, hypoplastic ovary, and high serum levels of FSH Animal studies using FSHR gene knockout mice showed cessation of folliculogenesis at prenatal stage. In addition, mutation in FSHR can lead to arrest of follicle development. Naturally occurring inactivating mutations in the FSHR gene have been reported in subjects with infertility. The phenotype of the infertile subjects has been well correlated with the extent of FSHR inactivation [10]. It is plausible that more subtle genetic variations of the receptor can contribute to functional perturbations, subfertility, and/or infertility.

In polycystic ovary syndrome (PCOS), dominant follicles fail to develop consistently. During the anovulatory cycles, there is a failure to up-regulate the expression of the aromatase enzyme in GC, and the estradiol concentration in the follicular microenvironment fails to increase adequately. Estrogen extends the action of FSH on granolosa cells by promoting their proliferation and increasing their expression of FSH receptor. These observations raise the question of whether abnormal Estrogen Receptor in polycystic ovaries affects them. Estrogen mediated by two receptors, the ER1, and the ER2. These belong to a superfamily of nuclear receptors that are ligand-dependent Tran's activators. The ER1 gene (140-kilo base) exists on chromosome 6q25.1 and consists of 8 exons; intron 1 contains single-nucleotide polymorphisms (SNPs) named the PvuII (T/C) (rs2234693). ER2 is located on chromosome 14q23.1 and comprises nine exons spanning about 62 kb. The 50 and 30 regions of the ER2 gene have common SNP polymorphisms: G/A exchange at nucleotide 1730 in the 30 untranslated region in exon 8 (AluI, rs4986938), and a silent 1082 G/A transition (16-20).
In view of regarding genotype rs6165 and rs6166 of FSHR and rs2234693 and rs4986938 of ESR1 and ESR2 we conducted case control study in Iranian women aged 20–40 yrs.

MATERIALS AND METHODS

Subjects

All subjects were recruited from the Fertility Center Shariati Hospital in Tehran, IRAN. The diagnostic criteria suggested by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) ESHRE/ASRM consensus conference [15] were used for PCO patients. 100 patients presenting with irregular menses, oligomenorrhea, or amenorrhea (without estrogen deficiency), particularly if there are also signs of hyperandrogenism, and 100 women with normal ovulatory function undergoing IVF for treatment of tubal and/or male infertility. Women were between 20 and 40 yr old. The study required no modification of our routine IVF protocol. All patients gave informed consent before their inclusion in this study. This study was approved by the Ethical committee of the Tarbiat Modares University, Tehran, Iran. For all patients SNPs analysis of 4 variants, 2 in FSHR {Thr307Ala (rs6165), Asn680Ser (rs6166)}, one in each ER1 PvuII T/C (rs2234693) and one in ER2 AluI G/A (rs4986938) has been done.

DNA isolation

A volume of 2-3 ml venous blood was drawn from each subject into a venoject containing EDTA as an anticoagulant. Genomic DNA was obtained from 100 µL of peripheral blood leukocytes with the DNPTM Kit Genomic DNA Purification Kit (SinaClon Co. IRAN) according to the manufacturer's instructions.

PCR-RFLP analysis

The PCR reaction was performed in a final volume of 25 µL containing 1 × PCR buffer, 1.5 mM MgCl2, 200 µM of each dNTP, 1 µM of each primer, 0.1 units of Taq-DNA polymerase (SinaClon Co. IRAN) and 200 ng of the DNA template were amplified for 35 cycles. A pair of primers was designed using Primer3 software (Whitehead Institute, Cambridge, Massachusetts, USA). Primer sets (takapouzist), annealing temperatures used for the PCR-RFLP assay are shown in Table 1. Afterwards, approximately 500 ng of amplified DNA was digested with following enzyme *BsrI, PvuII, Eco81I, AluI* (Fermentas) at their specific temperature according to Protocol overnight (Table 2). Restriction endonuclease digestion products were visualized, in 1.0% agarose gel for FSHR polymorphism and 2.0% agarose gel for ESR1 and ESR2. Sequence analyses was performed for tests with uninformative results.

Statistical analysis

Statistical analysis was performed using the chi-square test; program SPSS (version 17.0) Comparisons of the genotypic or allele frequencies between cases and controls. Analysis of Hardy-Weinburg Equilibrium was performed for all. Differences in continuous parameters between groups and genotypes were assessed with t-test. A conventional p value of ≤0.05 was considered as significant.

RESULTS

To examine the association between PCOS and the polymorphisms and to investigate the frequency of genotype, we used RFLP analysis as a tool in the FSHR, ESR1 and ESR2 gene, in the 100 PCOS patients and the 100 healthy controls. The patients mean age was 29.4 ± 4.9 years, while the mean age of the controls was 30.8 ± 3.9 years. Patients and control individual clinical and biochemical characteristics are shown in table 3.
First, RFLP analysis was performed for Ala307Thr variant has three genotypes (GG, GA, and AA), Homozygote GG found to be similar in PCOS patients, Homozygote AA observed in higher frequency in control group in contrast heterozygote of GA found more frequent in PCOS patient, (GG=33.0%, GA=42.0%, AA=25.0%) and the control group (GG=30.0%, GA=24.0%, AA=46.0%) .

RFLP analysis revealed the complete linkage between 307 and 680 amino acid transitions. The overall frequencies in PCOS patient, (GG=33.0%, GA=42.0%, AA=25.0%) and the control group (GG=30.0%, GA=24.0%, AA=46.0%), in PCOS population frequency of GA was significantly larger as compared with control group (Figure 1).

ER1 PvuII T/C SNPs located in intron 1, the distribution of PvuII genotypes among PCOS women undergoing IVF was as Follows: 29.0% were homozygous for TT, 49.0% were TC and 22.0% were homozygous for CC, with T and C allele frequencies of 52.3 and 47.7%, respectively AluI (1730G > A) polymorphism in the ER2 gene were detected by PCR amplification and AluI digestion. G Nucleotide was considered the wild-type sequence and was not digestible AluI. Genotype and allele frequencies of ER1 are as follow: TT, CC and TC frequency in PCOS patient are 29.0%, 22.0%, and 49.0% respectively that revealed the same frequency in control group with no significant deviation from Hardy–Weinberg expectations. (Figure 2)

Three genotypes were constructed for *AluI* (1730 A → G) (AA/AG/GG) polymorphic sites, based upon fragment patterns. Genotype frequencies of GG/AG/AA for ESR2 gene are presented in Table 4. AA frequency is similar between PCOS patient and control group. Frequency of GG and AG are slight different between groups. We did not observe associations of the functional SNPs in, ESR1 and ESR2 with the phenotype of PCOS or disease risk. (Figure 2)

Analysis revealed that the frequency of genotypes at position -29G/A, Thr307Ala, Asn680Ser, ER1 PvuII T/C and ER2 AluI G/A was in Hardy-Weinberg's equilibrium. Allele Frequency is shown in Table 4.

Table 1. Primers and PCR conditions used in the study

Gene	Sequence primers	Length(bp)	Annealing Temperature (C)	Polymerization time (sec)
FSHR307	**FORWARD, CAAGGGCAGGTATGATGTGAGAAG REVERSE, CTGATGCAATGAGCAGCAGGTAG**	**503**	**58**	**50**
FSHR68	**FORWARD, ATGTCATGTCCCTCCTTGTGCTC REVERSE, ATGTGTAGAAGCACTGTCAGCTC**	**510**	**58**	**50**
ESR1	**FORWARD, CATGAACCACCATGCTCAGTCTC REVERSE, CCACCCTGGCGTCGATTATCTG**	**586**	**58**	**60**
ESR2	**FORWARD, TGACCTGCTGCTGGAGATGCTG REVERSE, AGGCCATTGAGTGTGGAAACGC**	**330**	**60**	**30**

Table 2. Enzymes and incubation time and temperature used for digestion of PCR Products

Enzyme	Incubation temperature
Eco81I (Bsu36I)	37°C for 1-16 hours
PvuII	37°C for 1-16 hours
BseNI (BsrI)	65°C for 1-16 hours
AluI	37°C for 1-16 hours
MboII	37°C for 1-16 hours

Table 3. Clinical and biochemical characteristics between PCOS patients and normal controls

	Control group	PCOS patients
Number of subjects	**100**	**100**
AGE	**30.8 ± 3.9**	**29.4 ± 4.9**
Body Mass Index (kg/m^2)	**24.3 ± 4.6**	**26.9 ± 5.04**
FSH levels (mIU/ml)	**6.7 ± 2.8**	**7.4±3.7**
LH levels (mIU/ml)	**5.4 ±7.0**	**8.2±7.3**
E2 levels (pg/ml)	**41.8 ± 17.5**	**48.84 ± 27.0**
Cycle length (days)	**28.5 ± 2.6**	**26.7 ± 2.5**

Table 4. Allele Frequency of polymorphic variants in PCOS and control women

Gene	Variation	Allele	PCOS	Control	p Value
FSHR	Thr307Ala (rs6165)	GG GA AA	33.0% 42.0% 25.0%	30.0% 24.0% 46.0%	0.001
FSHR	Asn680Ser (rs6166)	GG GA AA	33.0% 42.0% 25.0%	30.0% 24.0% 46.0%	0.001
ESR1	PvuII T/C (rs2234693)	TT TC CC	29.0% 49.0% 22.0%	30.0% 48.0% 22.0%	0.871
ESR2	AluI G/A (rs4986938)	AA AG GG	15.0% 58.0% 27.0%	15.0% 48.0% 37.0%	0.336

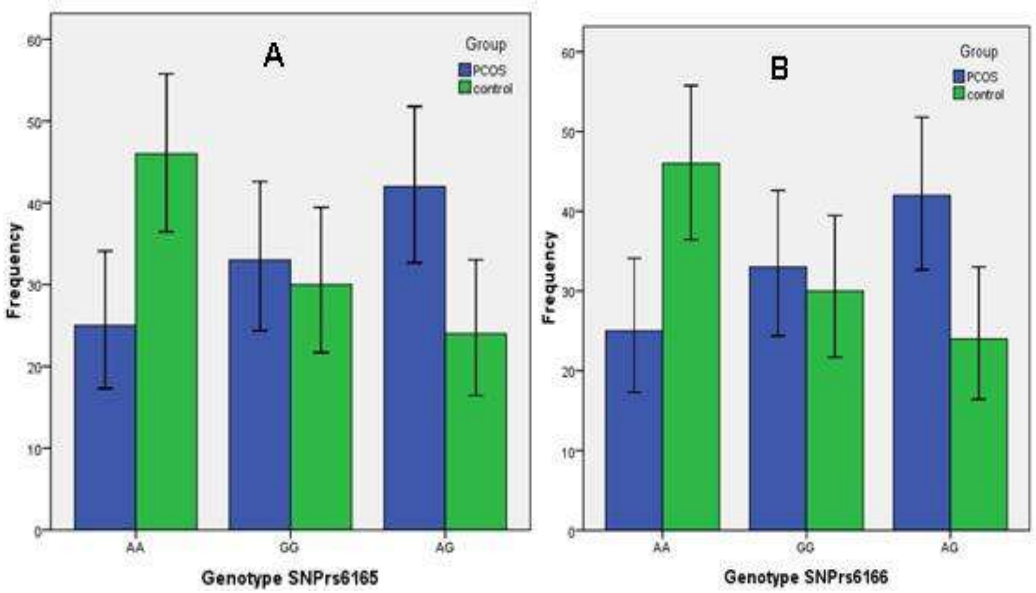

Figure 1A **Figure 1B**

Figure 1. Distribution of the single nucleotide polymorphism at position 307 (A) and 680 (B) of the FSH receptor gene analysis revealed the complete linkage between 307 and 680 amino acid transitions**.**

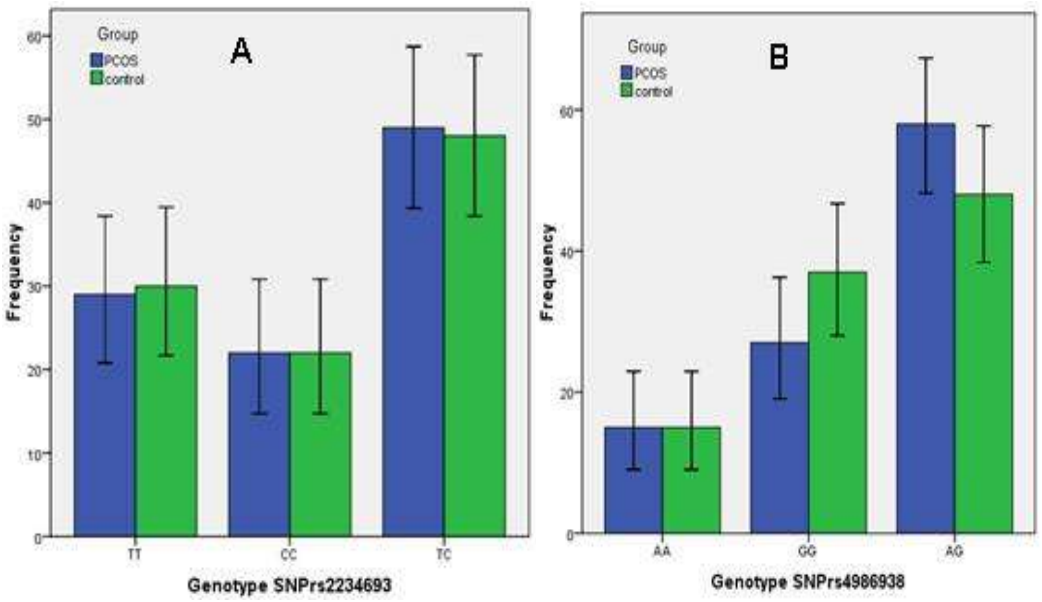

Figure 2A **Figure 2B**

Figure 2. Distribution of the single nucleotide polymorphism of ESR1 (A) and ESR2 (B) genes.

DISCUSSION

Polycystic ovary syndrome (PCOS), whose genetic basis is not completely well understood, is the most common endocrine disorder in women [5,18].There is clear evidence for an underlying genetic cause for PCOS based on familial clustering of cases and collectively data consistent with the concept that a gene or more likely several genes predispose to PCOS susceptibility (19). Despite involvement of numerous genes in PCOS patient it's clear that FSHR is one of the most important genes involved in this disease [7, 10, 18]. It's clear that regulation of FSH level is controlled by FSHR, and it is known that aberrant FSHR affects ovary and folliculogenesis. Genetic studies of FSHR gene in specific populations has been described in the past. To date, the common FSHR polymorphism Asn680Ser mostly in linkage disequilibrium with Ala307Thr is a well established determinant of response to FSH in IVF programs. In women, in vivo results suggest that the Ser680 genotype is a factor of major ''resistance'' to FSH stimulation, resulting in higher FSH serum levels, thus leading to prolonged duration of the menstrual cycle, although its role in vitro remains to be determined [7, 12,20, 22].

In this study we have selected most important genes that required for the developmental follicle, oocyte maturation, and regulation of steroidogenesis in the ovaries. Several studies have tried to correlate the frequency distribution of polymorphism in different genes with PCOS patient [27-31]. Therefore in order to develop real predictive genetic testing panel we increased the number of validated markers such as, FSHR 307, FSHR 680, ESR1, and ESR2 with the hypothesis that the abnormality in either these markers might be involved in abnormal follicle development in PCOS [32].

Most clinically relevant polymorphisms of FSHR gene are located in exon 10 at positions 307and 680, most studies were focused on position 680, whereas polymorphism 307 was rarely considered, in this study we investigate both SNPs. The genetic marker FSHR 680 is so far the most studied in relation to ovarian stimulation; however, the specificity and sensitivity of this genetic marker will be too low for it to be employed as predictive biomarker [6].

We showed that a polymorphism of Ala307Thr in FSHR appear more frequent in PCOS patient, the similar result found in previous research such as Sudo (21) who reported a significant increase in the Ala307Thr frequency among Japanese women with PCOS, 66.7% of which had such allelic variant in comparison to 43.5% of normally ovulating women. A significant association between the polymorphism Ala307Thr and PCOS was also reported by a recent study on Chinese women [32]. Interestingly in this study, the Ser680Asn polymorphism in FSHR appeared as a causative factor among PCOS patients in an Iranian population with frequency about 42% in PCOS patient. Several polymorphisms in FSHR correlated with PCOS are not yet clearly understood. To elucidate the importance of SNPs in FSHR in PCOS patients, further investigation with a large population of PCOS patients derived from different ethnic backgrounds is required. Our data revealed the statistically significant differences of Ala307-Ser680/Ala307-Ser680 genotype frequencies between two groups of patients and controls. Our results are in agreement with those obtained in other studies.

Estrogen receptors (ESRs) are important candidates in PCOS patient, since direct effects of estrogens on follicle growth, maturation and oocyte release are well established [9,18,20]. In addition to folliculogenesis, estrogens play an important role in endometrial preparation for implantation [17]. Estrogen signaling is mediated by estrogen receptors, which are ligand-activated transcription factors composed of several domains important for hormone binding, DNA binding and activation of transcription [19]. In folliculogenesis, the proliferative actions of estrogens are mediated by ER1 (predominantly expressed in the theca layer), while the differentiation and antiproliferative effects required for reaching the antral stage require ER2 (expressed in granulosa cells of growing follicles at all developmental stages [7, 9]. The ER1 PvuII locus is reportedly associated with the susceptibility to endometriosis [36] and COH/pregnancy outcome of IVF [6].

The ER1 gene is highly polymorphic, with more than 2200 SNPs, while around 720 SNPs in ER2 have been identified (www.snpper. chip.org). Polymorphism of ESR1 (rs2234693) was similarly distributed among PCOS patients and controls; also polymorphism of ESR2 (rs4986938) and frequency of AG genotype of ESR2 shows slightly different between PCOS and control group.

Our present study shows a statically significant association between genotype of three polymorphism of FSHR with PCOS. One of the major challenges for the clinician during IVF protocol is non availability of reliable predictive indicator to identify spender of women their genetic background. In the future, it should be possible tailor genetic therapy according to patient background and to design an individualized ovarian stimulation protocol in advance.

In conclusion evidence suggests that ovarian respond is mediated by various polymorphisms. To assess more subtle genetic effect in large sample size study in PCOS subjects is warranted to further investigate which genes and pathway could be involved.

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Conflicts of interests:

The authors declare no conflicts of interests.

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