Research Article

A Study on the Relationship between Polymorphism of the Selected Candidate Genes with Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome the most common gynecological endocrinopathy, is characterized by chronic anovulation and hyperandrogenism. It is commonly noted that people with polycystic ovary syndrome are closely related to obesity and insulin resistance. Several polymorphisms for such conditions have been hypothesized to be involved in its etiology, the present study deals with some of those genes. The main objective of the present study is to investigate the association of the following genes, FTO gene, TCF7L2 gene and PPAR γ gene with Polycystic Ovary Syndrome. In this study the single nucleotide polymorphisms of the above mentioned genes were studied in 30 normal samples and 30 PCOS samples using Tetra-primer amplification refractory mutation system polymer chain reaction (T-ARMS PCR).Among the SNPs analysed, the genotypic and allele frequencies has no significant association with Polycystic Ovary Syndrome. The results showed that no significance was found between the polymorphisms selected in controls and PCOS patients. A few more analysis on a longer cohort will reveal whether thus can be used as a marker for PCOS.

Key words: Polycystic ovary syndrome, Polymerase Chain Reaction, Single nucleotide polymorphism, Obesity, Insulin resistance.

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INTRODUCTION

PCOS is defined as a condition of uncertain etiology, with an indistinct pathophysiology and multiple endocrinal, reproductive and metabolic anomalies and is the single most common female disorder encountered in women of reproductive age.[1] According to Balen, the Polycystic ovary syndrome (PCOS) is a heterogeneous collection of signs and symptoms that, gathered together, form a spectrum of a disorder which leads to disturbances in the reproductive, endocrinal and metabolic functions of women.[2] As reported by Imani, PCOS patients have ovarian dysfunction, with 70% to 80% of women with oligomenorrhea or amenorrhea who are also positively correlated with infertility.[3] Hyperandrogenism is also considered as the most constant and prominent diagnostic component of polycystic ovary syndrome. The development of hirsutism, androgenic alopecia, acne, ovulatory dysfunction, etc., is observed in excess androgen secretion.[4] In 60% of women with polycystic ovary syndrome Hirsutism is the most common symptom.[5] The other metabolic features that influences PCOS includes dyslipidemia, obesity, cardiovascular disease and insulin resistance.

The prevalence of polycystic ovary syndrome in unselected populations of women of reproductive age is defined by the National Institutes of Health (NIH) criteria, as 6.5 to 8%.[5] Polycystic ovaries are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalence in the general population being in the order of

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20-33%.[6] The goals of treatment recommended by Samraj and Kuritzky variously include restoration of fertility, repair of objectionable signs of hyperandrogenism (e.g., acne, hirsutism), correction of metabolic abnormalities (including Dyslipidemia), avoidance of long-term sequelae (vide supra), menstrual regulation, and attention to psychological issues attendant to the disorder.[7] Xita *et al.* reported that 'PCOS appears to be an oligogenic disorder. Several genes involved in reproduction, genes affecting the secretion or action of insulin and those involved in obesity and energy regulation have been tested as candidate genes'.[8] They suggested the following candidate genes for PCOS selected from multiple biochemical pathways like steroid hormone biosynthesis or metabolism, gonadotropin action and regulation, obesity and energy regulation, insulin action.

A genome-wide association study discovered the fat mass and obesity-associated (FTO) gene as an obesity susceptibility gene.[9] FTO gene is a very large gene with nine exons span more than 400kb located on the long (q) arm of chromosome 16 at position 12.2.[10] FTO is highly expressed in brain regions such as the hypothalamus and act by controlling feeding and energy expenditure.[11] Several polymorphisms of the gene have been described. The variant FTO rs9939609 is located within the first FTO intron has two alleles A and T, the former has been linked to an increased risk of both obesity and type 2 diabetes mellitus.[12] The protein coded by FTO gene involving in energy metabolism belongs to 2-oxoglutarate-dependent nucleic acid demethylase.

TCF7L2 is a transcription factor in the want signalling pathway, which is critical for embryogenesis and cell proliferation, including development of the pancreas and islets. Associations between two SNPs, rs7903146 and rs12255372 (in intron 3 and 4, respectively) and T2DM have been replicated in numerous studies, and are the SNPs that provide among the strongest evidence of association with T2DM.[13] Most current evidence favours impaired insulin secretion as the result of Transcription Factor 7 Like 2 Associated Gene Polymorphism Associated with PCOS 59 mechanism responsible. The insulin resistance plays a major role in the aetiology of PCOS and there is evidence for a concomitant (potentially primary) disturbance of beta cell function. Hence endorsed as the biological candidate of TCF7L2 with respect to susceptibility to PCOS. PPARs are transcription factors that belong to the nuclear hormone receptor family. Reduced transcriptional activity of PPARγ is associated with an increase in insulin sensitivity.[14,15] The peroxisome proliferator activated receptor γ (PPARγ) gene is located at chromosomal region 3p25 and it is mainly expressed in the adipose tissue where it promotes the differentiation of preadipocytes into adipocytes.[16] The Pro12 Ala polymorphism of the PPARγ gene has been associated with reduced transcriptional activity of PPARγ and the presence of the Ala isoform has been linked to both higher insulin sensitivity and lower body mass index.[14]

In the present study, the single nucleotide polymorphisms (SNPs) of the above mentioned genes Table 1, were investigated in PCOS patients as well in the healthy controls.

MATERIALS AND METHODS

Collection of Samples

In this genetic study carried out at Dr. G R Damodaran College of Science, Coimbatore from July to December,

Table 1: Information the Designed Primers.

Candidate Genes	Primer Sequence (5' – 3')	TM(°C)	Amplication Size (bp)
FTO	OF---5'TGGCTCTTGAATGAAATAGGATTCAGAA-3' OR---5'AGCCTCTCTACCATCTTATGTCCAAACA-3' IF---5'TAGGTTCCTTGCGACTGCTGTGAATATA-3' IR---5'GAGTAACAGAGACTATCCAAGTGCATCTCA-3'	55	321
TCF7L2	OF---5'ATGAAAGAAGAAAGGCCTGCC-3' OR---5'GCACCTTCTGTCTCGGTTTC-3' IF---5'CAATAGGTTTTGAGGGGCATGA-3' IR---5'GAGGGCTGAACCCCGTCCC-3'	55	424
PPARγ	OF- --5'CCATATGTGCTTCCCCAGAC-3' OR---5'GGGTGGGAAACACACAAGAC-3' IF--- 5'GACAGATTGTCACGGAACAT-3' IR---5'GATCACCTGCAGTAGCTGCACG-3'	55	509

FTO is fat mass and obesity-associated (FTO) gene, **TCF7L2 is** transcription factor 7 like 2**, and PPARγ is** peroxisome proliferator-activated receptors

2019, all the 60 subjects were native to India and were females. The study population considered of two groups of women 1) clinically diagnosed with PCOS (*n*=30) and 2) normal healthy controls (*n*=30). The blood samples were collected with oral consent from ARMC, Thrissur, Kerala. Blood samples (5ml) were drawn after an overnight fast of 12-16 hr, using standardized laboratory techniques.

Clinical and Biochemical data

Clinical and Biochemical data, such as Body mass index (BMI), age, serum concentrations of Luteinising hormone (LH) and Follicle Stimulating Hormone (FSH), Glucose level, Cholesterol content, were collected from the study individuals. The comparison was done between the two groups of patients diagnosed with PCOS and normal healthy controls.

SNPs and polymorphism genotyping analysis

Selected polymorphisms were chosen from the NCBI site (http://genome.ucsc.edu/cgi-bin/hgPcr?command=start).

The specificity of all the primers was verified using *in silico* PCR. Both the primers were made to run on BLAST tool and thus the primers were selected based on the results in Table.

DNA was isolated using Split Second DNA isolation method

The reaction volume containing genomic DNA to be amplified and restricted contains 4µl nuclease free water, 1µl inner forward primer, 1 µl of inner reverse primer, 1µl of outer forward primer, 1µl outer reverse primer, 5µl template DNA, and 12 µl of amplicon. Tetra-primer amplification refractory mutation system polymer chain reaction (T-ARMS PCR) was performed using the thermal cycler as follows: an initial denaturation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 30 sec, annealing at 55°C for 30 sec, extension at 72°C for 30 sec and the final extension at 72°C for 5 min. All PCR products were visualized under UV light using by 2% agarose gel electrophoresis stained with ethidium bromide.

Statistical Analysis

To determine the significance of clinical and biochemical characters in the prognosis of polycystic ovary syndrome and to determine their impact on the development of the diseases statistical analysis were done using SPSS (Statistical package for social science) for windows version 16(IBM, USA) to determine the *p*-value. Comparisons between groups on continuous measures were made using the student t-test and a *p*-value of (<0.05) was considered significant at 95% levels of significance.

RESULTS AND DISCUSSION

Clinical and Biochemical data

The clinical and biochemical characteristics of the participants are showed in the Table 2. When looking into age as a clinical parameter it was found to be highly significant and it was found that the mean age of the PCOS patients (28.8±4.49) was higher than mean age of the normal controls (24.86±5.28). This may be due to the fact that a major problem faced by PCOS patients is that they have difficulty in conceiving and face infertility problems. Hence most of the samples collected are from women of child bearing age.

Studies by Chen *et al.* states that 'BMI is an acceptable representation of thinness and fatness, and has been directly related to health risks and death rates in many populations and also suggest that 'PCOS patient with a BMI of 23 kg/m2 or beyond may have risk of metabolic disorders.[17]' Studies by Yildiz and Mikola

Table 2: Clinical and Biochemical Data of the Study Participants.

Characterstics	Normal Control	PCOS	*p-Value*
Number	30	30	
Age	24.8±5.28	28.8±4.49	0.0025*
BMI	22.07±2.60	26.12±3.91	0.0000*
LH(mIU/ml)	4.20±1.866	10.93±3.95	0.0740
FSH(mIU/ml)	10.93±6.44	3.80±10.78	0.0089*
Cholesterol	190.93±50.28	224.3±35.97	0.0000*
Glucose	108.8±25.59	241.8±40.80	0.0711

Each value is given mean ± SD; *p-values* where significant at (*p*<0.05); *-Observation at *p*<0.05 on comparison of PCOS subjects with normal controls. BMI is Body mass index, LH is Luteinizing hormone, and FSH is Follicle stimulating hormone.

have suggested that the BMI was found to be high in patients with PCOS when compared to normal controls.[18,19] Our findings gave us a *p-value* of (0.000*) when normal patients are compared to PCOS patients. From this it can be inferred that PCOS patients are found to have a higher BMI when compared to normal patients. So increased BMI can be considered as a risk factor for PCOS.

According to Unluturk *et al.* 'Both increased LH levels and altered LH action are frequently observed in PCOS patients, and these abnormalities are associated with anovulation through, and this causes an adverse effect of LH on oocyte maturation'.[20] Many studies corroborate our findings.[21,22] From Table 2 it is very evident that there is no significance in the levels of LH and PCOS and the normal population. Our results are consistent with already established recommendations on an increase in LH levels in patients with PCOS and its determination may improve the prediction of the risk of PCOS.

The FSH is a gonadotropin, synthesized in the anterior pituitary gland which regulates the development, growth, pubertal maturation and reproductive processes of the body. FSH and LH act synergistically in the reproduction (2). In our study, the FSH levels were found to be higher in control groups when compared to the PCOS patients. These results are in accordance with the observations made by Dasgupta in Indian women.[23]

Legro *et al.* stated that 'Women with polycystic ovary syndrome are profoundly insulin resistant, and the resultant hyperinsulinemia exacerbates the reproductive abnormalities of the syndrome.[24]' Women with PCOS also have an increased risk of developing glucose intolerance, T2DM.[25] Our results are supported by a number of studies in which the researchers have found significantly higher levels of glucose when compared to controls.

According to The National Cholesterol Education Program (NCEP) Individuals with Polycystic Ovarian Syndrome (PCOS) are at increased risk of high levels of LDL "bad" cholesterol, which, if neglected, can have an adverse impact on cardiovascular health. Conversely, women with PCOS often also have lower levels of HDL "good" cholesterol, which is another risk factor to cardiovascular health. As expected, the levels of cholesterol analysed where significantly higher in PCOS when compared to the controls.

Genotype Analysis

All the gene variants were successfully amplified in all the 60 study population using T-ARMS PCR method. For FTO gene, the presence of T allele was detected by a 178bp amplicon and A allele was detected by a 201bp amplicon. The product size of the outer primers is 321 bp. The presence of homozygous AT genotype gave a banding pattern of 321bp, 201bp and 178bp (Figure 1). The chi square analysis of the genome variants revealed that the variant rs9939609 of the FTO gene was not highly significant for the association with PCOS. The polymorphic A allele was found to be a risk factor for PCOS. The prevalence of the polymorphic A allele was 70% when compared to its prevalence of 30% for the control women. The prevalence of the T allele was 30% when compared to its prevalence of 33.6% for the control women. Do Kyung in his study found an association of FTO polymorphism with an increased risk of PCOS and hyperandrogenaemia in young Korean population.[26] The rs9939609 variant of the FTO gene were found to be associated with the increased susceptibility in the UK and the Chinese population, but the variant rs734312 0f the FTO gene has no significant association with PCOS. Most of the studies carried out on various different populations identified a significant association of FTO polymorphism with higher BMI levels.

For TCF7L2 gene, the presence of T allele was detected by a 272bp amplicon and C allele was detected by a 202bp amplicon. The product size of the outer primers is 424 bp. The presence of homozygous TC genotype gave a banding pattern of 424bp, 202bp and 272bp (Figure 2). The chi square analysis of the genome variant rs12255372 of the TCF7L2 gene also revealed that the variant was not highly significant for the association with PCOS. The prevalence of the polymorphic T allele was 71.6% when compared to its prevalence of 45% for the control women. The prevalence of the C allele was 28.3% when compared to its prevalence of 38.3% for the control women. Groves and his co-workers

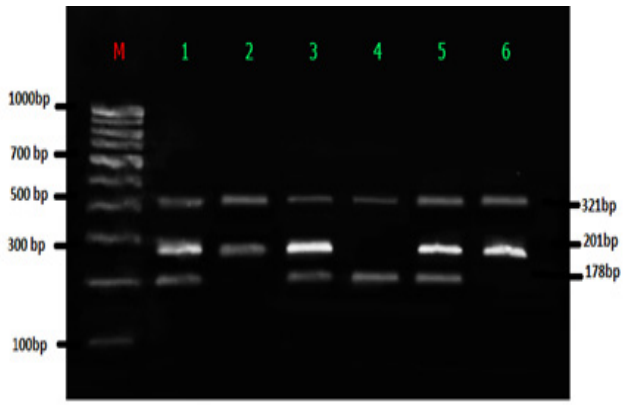

Figure 1: T-ARMS PCR Analysis of FTO gene. (M) - 100 bp Molecular marker; Lane1, 3, 6 (AT-321 bp, 210 bp, 178bp); Lane 2,5(TT-321bp, 178 bp); Lane 4 (AA-321 bp, 201bp).

and Song *et al.* reported the 'Associations between two SNPs, rs7903146 and rs12255372 (in intron 3 and 4, respectively) and T2DM have been replicated in numerous studies, and are the SNPs that provide among the strongest evidence of association with T2DM.[13,27]' Barber was the first to test associations between the two T2DM associated SNPs in two large data sets; one is a UK British/Irish cohort of 369 PCOS cases and 2574 controls, and the second set of 540 women with PCOS symptoms and 1083 controls chosen from the Northern Finland Birth Cohort of 1966. However, they did not find a significant association either with PCOS or androgen levels; and therefore concluded that genetic variation influencing b-cell function is not a major predictor of PCOS pathogenesis.[28]

For PPARγ gene, the presence of T allele was detected by a 350bp ampicon and C allele was detected by a 200bp amplicon. The product size of the outer primers is 509bp. The presence of homozygous CT genotype gave a banding pattern of 509bp, 350bp and 200bp (Figure 3).The chi square analysis of the genome variants revealed that the variant rs3856806 of the PPAR-γ gene was not highly significant for the association with PCOS. The polymorphic C allele was found to be a risk factor for PCOS. The prevalence of the polymorphic C allele was 75.4% when compared to its prevalence of 25.6% for the control women. The prevalence of the T allele was 45% when compared to its prevalence of 55.5% for the control women. In a Turkish population Tok showed that 'the prevalence of PPAR- γ polymorphism was 10% in women with PCOS and 22% in control subjects, but they did not find significant differences between PCOS and control subjects because of their small sample size'.[29] Orio and colleagues determined 'the prevalence of PPAR-g Pro12Ala polymorphism to be similar in PCOS and control subjects (5.9 vs. 4.2%, respectively)'.[30] Likewise, Hahn and associates in the year 2005 also found 'the prevalence of Pro12Ala polymorphism of PPAR-g in PCOS subjects (22.5%) to be similar to that in controls (23.1%)'.[31]

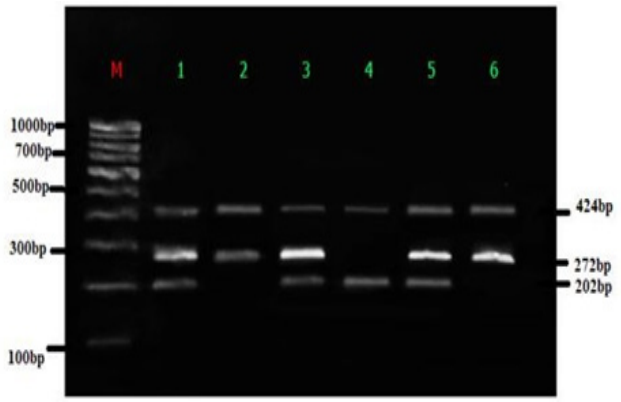

Figure 2: T-ARMS PCR Analysis of TCF7L2 gene. (M)- 100 bp Molecular marker; Lane1, 3, 5 (CT-424 bp, 202 bp, 272bp); Lane 2,5 (TT-424bp, 272 bp); Lane 4 (AA-424 bp, 202bp).

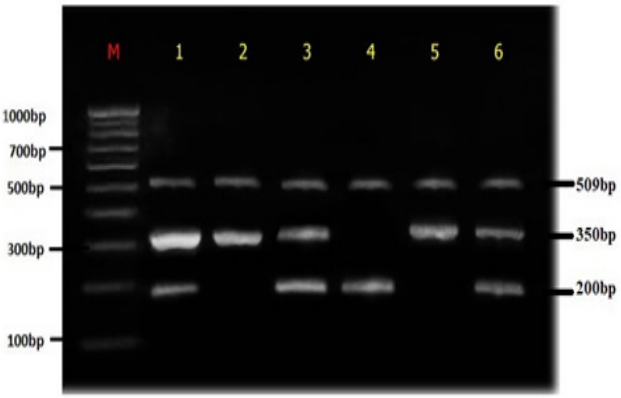

Figure 3: T-ARMS PCR Analysis of PPARγ gene. (M)-100 bp Molecular marker; Lane1, 3, 6 (CT-509bp, 201 bp, 350bp); Lane 2, 5(CC-509bp, 200bp); Lane 4 (TT-509 bp, 350bp).

CONCLUSION

The determining of SNPs associated with PCOS will help researchers understand the complicated pathophysiology associated with PCOS. Our study was undertaken to scan out for unique polymorphisms of the FTO gene, TCF7L2 gene and PPARγ gene which could be used in diagnosis and screening of PCOS. But the results showed that no significance was found between the polymorphisms selected in controls and PCOS patients. A few more analysis on a longer cohort will reveal whether thus can be used as a marker for PCOS.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

w/v: Weight/Volume; **μg:** Microgram; **μl:** Microliter; **BMI:** Body Mass Index; **Bp:** Base pair; **DNA:** Deoxyribo Nucleic Acid; **dNTP's:** Deoxyribo Nucleotide Tri-phosphates; **EDTA:** Ethylene Diamine Tetra Acetic acid; **FSH:** Follicle Stimulating Hormone; **LH:** Luteinizing Hormone; **Kg:** Kilogram; **Mg:** Milligram; **Ml:** Milliliter; **mM:** Millimolar; **mMOL:**

Millimolar; **PCOS:** Polycystic Ovary Syndrome; **PCR:** Polymerase Chain Reaction; **SNP:** Single Nucleotide Polymorphism; **TBE:** Tris Borate EDTA; **FTO:** Fat Mass and Obesity; **TCF7L2:** Transcription factor 7-like 2; **PPARγ:** Peroxisome proliferator-activated receptor gamma.

SUMMARY

PCOS is right now the biggest health concern faced by women of reproductive age with alarming incident rates. What makes PCOS a disturbing problem is that 70% of the women diagnosed with PCOS end up being infertile. PCOS onset happens at a relatively young age with evidence claiming that environment factors aggravate the symptoms of the syndrome. The exact causes of PCOS are still a mystery even after being first identified almost 70 years ago. A lot of studies have not been obtained. With infertility being an exponential increase and a major cause being PCOS in women, its early detection and treatment have very significant roles in improving the standards of life.

Hence this study was undertaken to scan out for unique polymorphisms of the selected candidate gene which could be used in diagnosis and screening of PCOS. In this regard Blood samples were collected from infertile women who have been diagnosed with PCOS. A normal control group was also employed who were the healthy controls without PCOS. Different polymorphisms were analyzed for the selected candidate genes. Biochemical parameters were compared for all the 60 subjects involved in the study. Hormonal and clinical parameters were compared using student *t*-test and genotypic and allelic markers were analyzed using chi-square analysis.

The BMI was found to be much higher in the patients with PCOS when compared to the normal and healthy controls. The levels of the LH hormone was many folds higher in PCOS subjects when compared to the controls indicating that high LH levels could be used as an indicators of PCOS .The levels of FSH showed significant differences in the population studied. In this study the polymorphisms of the selected candidate genes were not found to be associated with an increased risk for PCOS in the population studied.

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