SUMMARY

Endometriosis is one of the major threats to women's health that leads toward infertility. The inheritable predisposition to endometriosis develops a growing interest in identifying the genes and genomic variants involved in the pathogenesis of endometriosis. Polycystic ovary syndrome (PCOS) is the major cause of anovulatory infertility. The genetic basis of PCOS is not well understood, it is a common metabolic and endocrine disorder. The current study aimed to investigate for the first time, the possible genomic variants and single nucleotide polymorphism (SNP) in selective genes associated with endometriosis and PCOS in Pakistani women from the Punjab region. DNA samples from fifty-two genetically unrelated endometriosis patients and fifty-two controls were analyzed by direct sequencing to determine the polymorphisms of estrogen receptor alpha *ESR1* (rs2234693, rs9340799), estrogen receptor beta *ESR2* (rs4986938), progesterone receptor *PGR* (rs1042838, rs10895068), interleukin 10 *IL10* (rs1800871, rs1800872 and rs1800896) and follicle stimulating hormone receptor *FSHR* (rs6166, rs6165) genes. Genetically unrelated PCOS patients and controls, 96 each, were selected on the basis of their Body Mass Index (BMI) and degree of obesity. The polymorphisms of different loci on adiponectin *ADIPOQ* (rs2241766, rs1501299 and rs2241767), insulin receptor *INSR* (rs1799817, rs1799815 of rs2059806 and rs2229429), *FSHR* (rs6164, rs6165), Follicle stimulating hormone beta *FSHB* (rs6169), Luteinizing hormone choriogonadotropin receptor *LHCGR* (rs61996318 and rs111834744), Luteinizing hormone beta *LHB* (rs1800447 and rs4002462), *ESR1* (rs2234693, rs9340799) and *ESR2* (rs4986938) genes were analyzed by direct sequencing. The rs4986938 of *ESR2* and rs1042838 of *PGR* gene show strong association ($p = 0.006$, *OR*: 1.360; *CI*: 0.16-0.80; $p < 0.003$, $OR = 1.935$, 95% $CI = 0.10$-0.62) with endometriosis. The genotype and allele frequency of *ESR1* gene polymorphisms were distributed similarly among patients and control groups ($p > 0.050$). The allele A of rs1800872 ($p < 0.006$, $OR = 2.379$, 95% $CI = 0.23$-0.75), T of rs1800871 ($p = 0.010$, $OR = 0.443$, 95% $CI = 0.19$-0.92) and G of rs1800896 (($p = 0.007$, $OR = 1.435$, 95% $CI = 0.24$-0.77) at *IL10* gene were strongly associated with the predisposition of endometriosis in Pakistani women. Significant ($p < 0.001$) associations were observed within the genotype frequencies, allele frequencies and multi-SNP haplotype analysis of the genetic polymorphisms of *FSHR* gene with endometriosis. This study identified new single nucleotide

polymorphisms (SNPs) at positions +349 A/G in *ADIPOQ*, +1638 T/C in *INSR* and +657 del/T in *LHCGR* genes associated with PCOS ($p < 0.005$) in Pakistani women. The polymorphisms in the *ADIPOQ* ($r^2 = 0.78$), *ESR1* ($r^2 = 0.48$) and *FSHR* ($r^2 = 0.76$) genes were in strong ($p < 0.001$) linkage disequilibrium. The highly significant ($p = 0.030$, *OR* = 0.436, 95% *CI* = 0.21-0.89) SNP of *ADIOPQ* gene associated with PCOS was rs2241766 when compared with their controls. In *INSR* gene the most common haplotypes CGT, CAC and CAT were found to be more prevalent in the PCOS than controls ($p < 0.001$). The *FSHR* and *LHB* gene polymorphism seems to be stable loci in Pakistani PCOS women ($p > 0.050$). Whereas, the rs6169 of *FSHB* gene was strongly ($p = 0.020$, *OR* = 0.606, 95% *CI* = 0.40-0.91) associated with PCOS in this subpopulation. The rs111834744 of *LHCGR* ($p < 0.001$, *OR* = 1.270, 95% *CI* = 0.18-0.42), rs2232693 of *ESR1* and rs4986938 of *ESR2* genes were significantly ($p < 0.005$) associated with the onset of PCOS in Pakistani women. Significant ($p < 0.005$) associations were observed within the genotype frequencies, allele frequencies and multi-SNP haplotype analysis of most polymorphisms studied. Serum progesterone level was lower in endometriosis patients while the serum testosterone and FSH titres were higher in PCOS women when compared with their controls ($p < 0.001$). The current findings suggest that the functional promoter polymorphism of *IL10* gene ATG genotype may contribute in the risk of endometriosis. Current study provides the novel and new to science associations of *ADIPOQ, INSR, FSHB, LHCGR, ESR1* and *ESR2* genes with PCOS in Pakistani women. The genetic variants of above mentioned gene loci might influence the fertility status of endometriosis and PCOS patients. This suggests that the susceptible loci for endometriosis and PCOS lie within or very close to the chromosomal regions spanning these genes.