SUMMARY

PCOS continues to be of major women’s health concern worldwide. It is the leading cause of female infertility. It is also considered as one of the most common and a complex female endocrine disorder. Understanding the genetics of these complex and multifactorial disorder is a challenging facet. Ascertaining the variations in genes that contribute to the complexity of disease will aid as a basis for understanding the genetic basis of the disease variability in drug response across individuals/populations, as well as discovery of potential drug targets. Single nucleotide polymorphisms (SNPs) are the most common cause of human genetic variations. Of which, the missense SNPs (that cause a change in protein sequence) accounts for more than half of all genetic polymorphisms known to cause inherited diseases.

The analysis of single nucleotide polymorphism on multiple selected genes reveal that rs1801278 (Gly972Arg) of IRS1 gene showed a stronger and a significant association with PCOS. Polymorphism of Gly972Arg may perhaps play a contributory role in the pathophysiology and risk of PCOS. We observed the homozygous genotype (AA) for the polymorphic allele rs1801278 of IRS1 gene to be associated with a 2.88-fold increase in risk for PCOS as compared to the TT genotype. IRS1-rs1801278 is an important functional SNP involved in the insulin signaling by activating phosphatidylinositol-3-kinase (PI3K) a vital step in the commencement of several effects of insulin such as glucose transport and reported to be associated with insulin resistance, type2 DM and PCOS. Other specific
associated genes did not show an association with disease susceptibility but may play a synergistic role, leading to heterogeneous pathophysiological changes.

Association analysis (using allelic model) carried on PCOS women positive for insulin resistance compared with control women disclose there is a 1.92-fold increased risk of A allele in the polymorphism rs1801278 of IRS1 gene and a 2.27-fold increased risk of A allele in the polymorphism rs2975766 of CAPN10 gene in PCOS women with insulin resistance compared to the control women.

Further, PCOS women were grouped into insulin resistant and non-insulin resistant and were assessed to find any association between single nucleotide polymorphism of genes in PCOS women with insulin resistant compared with PCOS women with non-insulin resistant. We observed a 20-fold increased risk of A allele in the polymorphism rs689 of INS gene and a 2.14-fold increased risk of A allele in the polymorphism rs1801278 of IRS1 gene in PCOS women with insulin resistance than PCOS women who do not have insulin resistance. Moreover, a 0.05-fold decreased risk was observed in the polymorphism rs1801282 of PPAR-G gene in PCOS women with insulin resistant compared to non-insulin resistant PCOS women presenting its protective nature. In all of the categories analyzed IRS1–rs1801278 was found to play a vital role in the manifestation of PCOS in our studied population. Further analysis of this SNP variant should be evaluated in larger population and the same variant should be checked in different population groups to confirm its significance. Also, additional SNPs of IRS1 gene has to be studied to confirm the role of insulin receptor substrate 1 gene towards PCOS.
We also observed that the genotypes have a link on the phenotypic trait. Implication of genetic factors did contribute to insulin resistance in the pathogenesis of polycystic ovarian syndrome in the studied population. The single nucleotide polymorphisms majorly influenced insulin resistant in PCOS women with raised insulin levels, elevated fasting glucose and post-prandial glucose levels. In the presence of peripheral insulin resistance, pancreatic β-cell insulin secretion increases in a compensatory fashion, leading to a hyperinsulinaemic state. The genotypes also reflected lower insulin sensitivity in PCOS women. Also alterations in levels of LH, LH/FSH ratio, ovarian volume and antral follicular count were observed including an increase in body mass index and waist/hip ratio in PCOS women. We also observed gene to gene interaction between genes \textit{INSR} (rs1799817), \textit{IRSI} (rs1801278) and \textit{PPAR-G} (rs3856806).

The study on single nucleotide polymorphisms of \textit{INS} (rs689), \textit{IRSI} (rs1801276), \textit{IRS2} (rs1805097), \textit{CAPN10} (rs7607759), \textit{CAPN10} (rs295766) genes on polycystic ovary syndrome is the first of its kind to be carried out in the Indian population. Identification of these SNPs in PCOS population might give an insight in offering therapy in the form of insulin sensitizers. It can be proposed that recognizing the subset of young PCOS women who might benefit by insulin sensitizer therapy would aid the clinician in offering insulin sensitizers to young PCOS women with infertility.