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Small molecule-based modulation of sex hormone binding globulin gene expression as a potential therapeutic approach for polycystic ovarian syndrome.

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Polycystic ovarian syndrome (PCOS) is a complex endocrine and metabolic disorder that affects women of reproductive and child bearing age. One of the major characteristics of PCOS is hyperandrogenism which contributes to reproductive and metabolic complications seen in PCOS. Sex hormone binding globulin (SHBG) is a glycoprotein that in part regulates the androgen levels by sponging the free androgens through direct binding. Women with PCOS are reported to have low levels of SHBG which results in increased amounts of free and metabolically active androgens that cause hormonal imbalance. We hypothesize that by upregulating the levels of SHBG one can reduce the androgen levels and alleviate PCOS related symptoms and complications. In this study, to regulate the expression levels of SHBG the binding mode of competing transcription factor, the peroxisome proliferator-activated receptor gamma-2 (PPARγ-2), to the promoter of SHBG is analyzed using computational biology and a small molecule is designed to competitively inhibit the PPARG-2 from binding the SHBG promoter with a goal to decrease the blood levels of free androgens.

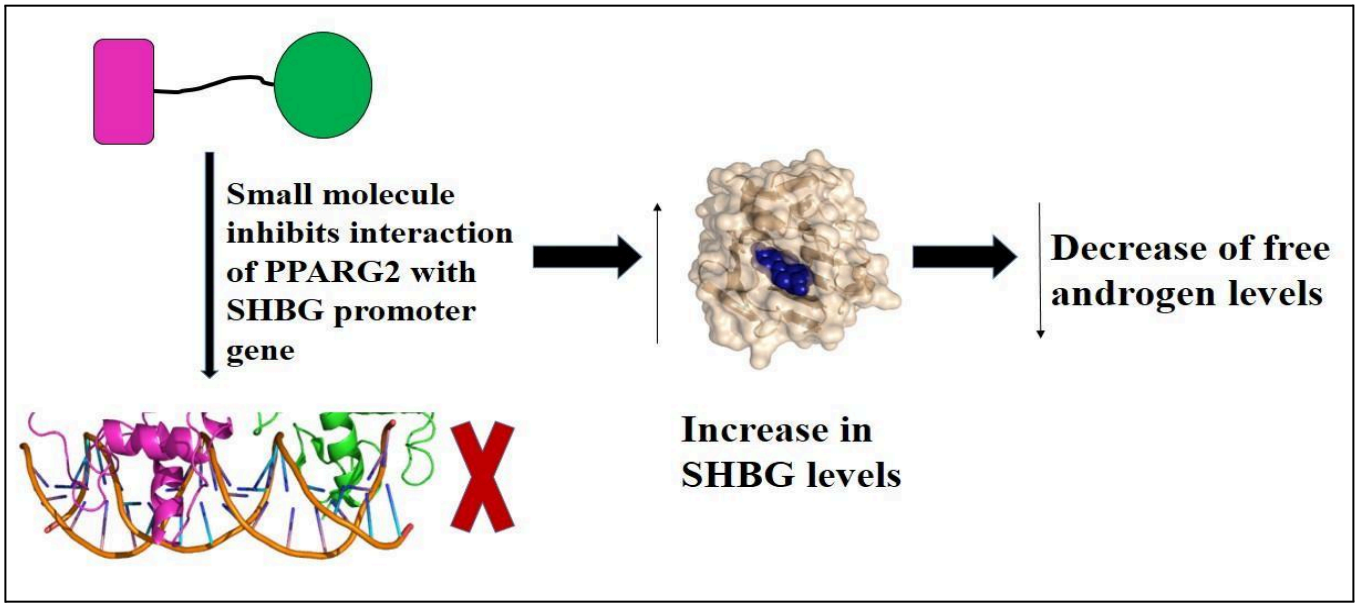

Figure 1. Overall strategy for analyzing the PPARγ-2 binding profile to the SHBG promoter and design of small molecule inhibitor.

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Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder. By considering Rotterdam diagnostic criteria, PCOS affects about 6-13% of reproductive aged women globally, as per World Health Organization (WHO, 2025). In India the prevalence of PCOS is estimated to be 19.6% [1]. As per Rotterdam consensus, PCOS is defined by the presence of any two of the following three features: Oligo- or anovulation, hyperandrogenism and polycystic ovaries [2]. Women with PCOS have elevated levels of androgens, insulin, serum luteinizing hormone (LH),

increased luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio and low levels of estrogen and growth factors [3]. These hormonal imbalances have both reproductive and metabolic implications. The reproductive implications include chronic anovulation, menstrual irregularities, poor pregnancy rates, adverse pregnancy outcomes, infertility and a higher risk of developing endometrial cancer [4, 5] whereas the metabolic implications include hyperinsulinemia, insulin resistance, obesity, increased risk of type-2 Diabetes, dyslipidemia and cardiovascular diseases [6].

Hyperandrogenism is a major characteristic of PCOS. It clinically manifests as hirsutism, acne, androgenic alopecia and as acanthosis nigricans. Hyperandrogenism is known to impact folliculogenesis, menstrual cycles and endometrial function, leading to reproductive problems [7]. The excessive androgen exposure on important peripheral tissues like adipose, liver, pancreas, muscle and brain plays a prominent role in development of a multitude of metabolic complications observed in PCOS [8]. The androgen excess is a result of both ovarian and adrenal overproduction. Excessive LH and a disrupted LH/FSH ratio observed in PCOS stimulates the overproduction of androgens by ovarian theca cells [7]. Both ovaries and adrenal glands have insulin receptors, the hyperinsulinemic condition of PCOS women leads to overstimulation of ovarian theca cells and enhancement of adrenal production of androgens[9, 10]. Along with these factors low levels of sex hormone binding globulin (SHBG) observed in PCOS women also contributes to increased bioavailability of androgens [11].

Sex steroids produced at various sites in the body are carried through blood to their target sites by steroid binding proteins. The main androgen testosterone is carried by two binding proteins namely SHBG and albumin. Ninety eight percent of circulating testosterone remains bound to SHBG and albumin in metabolically inactive form, only 2-3% remains unbound and metabolically active. SHBG has a higher affinity to bind to testosterone than that of albumin [11]. This higher affinity makes SHBG a primary plasma transport protein that regulates bioavailability of testosterone. Multiple studies have shown that SHBG levels in PCOS women are significantly lower than that of women without PCOS [12-14]. Low levels of SHBG leads to increased free and metabolically active testosterone in the blood stream, which contributes to the hyperandrogenic state seen in PCOS. Low levels of SHBG is associated with high risk of metabolic syndrome, lipid disorders and insulin resistance. SHBG is considered as an important biomarker for metabolic abnormalities observed in PCOS [11, 15]. Up regulation of SHBG levels can help reduce free androgen levels and alleviate PCOS related symptoms and complications.

Hepatocytes are the major site for SHBG production. Hepatocyte nuclear factor 4α (HNF-4α) is an important transcription factor in SHBG production, it activates SHBG synthesis in the liver by binding to two DR1 *cis*-element-binding sites in the SHBG proximal promoter region. Peroxisome proliferator activated receptor gamma-2 (PPARγ-2) and chicken ova upstream promoter–transcription factor 1 (COUP TF 1) compete for the same binding sites as that of HNF-4α. When PPARγ-2 and COUP TF-1 bind to the DR1 sites, the transcription of SHBG gene is suppressed, as a result the serum SHBG levels are decreased [16]. We hypothesize that if one can design small molecules that would interfere with PPARγ-2 and/or COUP–TF1 binding to the promoters of SHBG then it would be possible to increase the expression levels of SHBG.

This study focuses on the transcriptional factor PPARγ-2. In order to understand the interaction of PPARγ-2 with DNA, analysis of DNA bound PPARγ-2 structure was performed using computational biology tools. Structure of DNA bound PPARγ-2 was downloaded from the protein data bank (PDB ID 3DZY). The analysis includes evaluation of secondary structure (α helices and β strands) using PyMOL molecular graphics software. Hydrogen bond analysis was performed using PyMOL. All hydrogen bonds between DNA and PPARγ-2 were listed (Table 1) and analyzed further. The analysis revealed that PPARγ-2 is a dimer that binds to DNA through multiple hydrogen bonds, with each monomer making contacts in both the minor and major grooves of DNA. The bond lengths of hydrogen bonds between PPARγ-2 and DNA were found to be within the range of 2.4 Å to 3.4 Å, making the average bond length 2.9 Å. The hydrogen bonds with bond length less than 3 Å were considered as strong hydrogen bonds, so it concludes that the PPARγ-2 forms strong interaction with DNA. Based on these findings, a small molecule is designed which will be synthesized and evaluated *in vitro* and *in vivo*. All data will be published in the future issues of TCABSE-J.

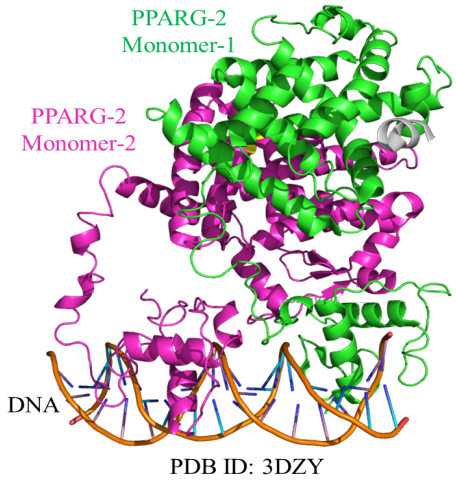

Figure 2. Structure of PPARγ-2 bound to DNA.

Nucleotide	Bond length	Amino acid
DT3006	2.9 Å	Phe121
DA3007	2.7 Å	Tyr123
DG3008	3.1 Å	Tyr123
DA4011	3.0 Å	Glu129
DG3008	3.0 Å	Lys132
DG3008	3.3 Å	Lys132
DT4009	3.0 Å	Arg137
DT4009	3.3 Å	Asn160
DG4010	3.4 Å	Asn160
DG4010	3.0 Å	Arg166
DG4010	3.1 Å	Arg166
DG4010	2.5 Å	Arg159
DT4009	2.7 Å	Gln163
DA4015	3.4 Å	Gly183
DA3014	2.6 Å	Tyr147
DA3015	2.8 Å	Tyr147
DC4005	2.8 Å	Glu153
DT4002	2.7 Å	Arg161
DT4002	3.1 Å	Arg161
DG3016	2.3 Å	Arg164
DG3015	2.9 Å	Arg164
DG4003	2.4 Å	Arg184
DG4003	3.2 Å	Arg184
DG4003	2.9 Å	Asn185
DG4003	3.1 Å	Arg199
DG4003	3.3 Å	Arg199
DA3014	3.2 Å	Gln206
DG3015	3.1 Å	Gln206
DT3010	2.9 Å	Gln206
DG3016	2.4 Å	Glu208

Table 1. List of hydrogen bonds/interactions between PPARγ-2 and DNA.

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Conflict of interest: The authors declare no conflict of interest in this study.

Author contributions: L.U. performed the work under the guidance and supervision of R.S.Y. R.S.Y. is the principal investigator who designed the project, trained L.U., secured required material for the project, provided the laboratory space and facilities needed. R.S.Y. wrote, edited and finalized the manuscript.

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