Original Article

BMP15 expression in silico analysis of rs377085803 (Ile90Thr) in polycystic ovary syndrome women

Mustafa Ihsan Al-Mahroos[1], **Duaa Jaafar Al-Tamimi**[2*], **Hasanain Amer Naji**[3]

[1]College of Pharmacy, Al-Farahidi University, Baghdad, Iraq. [2]College of Pharmacy, Madenat Alelem University, Ministry of Higher Education and Scientific Research, Baghdad, Iraq. [3]College of Pharmacy, Al-Turath University, Baghdad, Iraq.

Correspondence: Duaa Jaafar Al-Tamimi, College of Pharmacy, Madenat Alelem University, Ministry of Higher Education and Scientific Research, Baghdad, Iraq. duaa.jaafar@mauc.edu.iq

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ABSTRACT

The present study aimed to examine the expression of the BMP15 gene and the presence of a specific single-nucleotide polymorphism (SNP), rs377085803 (T/C), in Iraqi women with polycystic ovary syndrome (PCOS). The blood samples were collected from 50 infertile women diagnosed with PCOS and 50 healthy fertile controls attending Al-Elwiya Education Hospital and Al-Kadhimiya Teaching Hospital in Baghdad, Iraq. Reverse transcription quantitative polymerase chain reaction (RT-qPCR), DNA sequencing, and bioinformatics tools were used to analyse BMP15 gene expression and evaluate the potential impact of the SNP on protein structure. BMP15 gene expression was significantly downregulated in PCOS patients compared with controls(expression value: 0.507 vs. 1.000, $p=0.001$). Significant differences in genotype and allele frequencies were also observed between the two groups, with the heterozygous TC genotype of rs377085803 occurring more frequently in PCOS patients. This SNP is located in the pro region of the BMP15 protein and may influence protein folding and function. The findings of these results highlight the potential role of BMP15 gene alterations in the pathophysiology of PCOS. Genetic variation in BMP15 may contribute to reproductive dysfunction, although further studies with larger sample sizes are required to confirm these results.

Keywords: *BMP15* gene, Single-nucleotide polymorphisms (SNPS), rs377085803, PCOS, Molecular docking

Introduction

Infertility is a common health problem among adults aged 20 to 45 years globally and represents a major public health issue [1]; more than half of the infertile women exhibit no discernible cause, often presenting with idiopathic infertility, which may stem from inherited or acquired conditions. While the exact mechanism of interaction remains unclear, numerous contributing factors have been suggested, including genetics [2], immune system dysfunction, environmental impact, and hormonal imbalances [3]. Infertility is an escalating social concern often involving both male and female partners, particularly in industrialised countries, impacting both families and communities because one in eight couples struggle to conceive their first child, and about one in six face infertility when attempting to have other children. Among the multiple contributing factors causing infertility, genes of the transforming growth factor-beta (*TGFβ*) superfamily are vitally crucial for female fertility via interacting with transmembrane serine/threonine kinase receptors, thereby influencing various developmental processes such as cell proliferation, differentiation, and adhesion [4]. This super family includes three main categories of genes: proteins such as active receptor-like kinase 6 (ALK6), differentiation factor-9 (*GDF9*), and the bone morphogenetic proteins (*BMP*) family [5]. Bone morphogenetic

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protein 15 (*BMP 15*) represents the major gene category within the *TGFβ* superfamily, which recent research has shown to have roles in PCOS-related female infertility because it is critical in follicle development and oocyte competence [6]. The *BMP15* gene is located on the short arm (P) of the X chromosome at position 11.22, which encodes the Bone morphogenetic protein 15 [7]. This gene contains two exons, the first exon encodes for 109 amino acids, while the second exon encodes for 283 amino acids, together producing the *BMP15* protein, which contains 392 amino acids that form the homo-dimer structure of the protein with a Molecular mass of approximately 45055 Da. *BMP15* is expressed in the gonads and plays a key role in folliculogenesis and embryonic development [8]. The genetic variation of *BMP15* can be associated with conditions such as ovarian dysgenesis and polycystic ovary syndrome (PCOS). Polymorphisms could also cause alterations in transcription and protein expression in the first exon of the *BMP15* gene [9]. To date, limited research has explored the potential association between female infertility and the *BMP15* gene [10]. The present study aimed to evaluate BMP15 gene expression and investigate the association of the rs377085803(T to C; Ile90Thr) variant with PCOS in Iraqi women, as well as to predict the potential structural effect of this variant using in silico analysis.

Computational strategy and materials

The methodology comprises several techniques and phases. An overview of the methodology is displayed in the flowchart **(Figure 1)**.

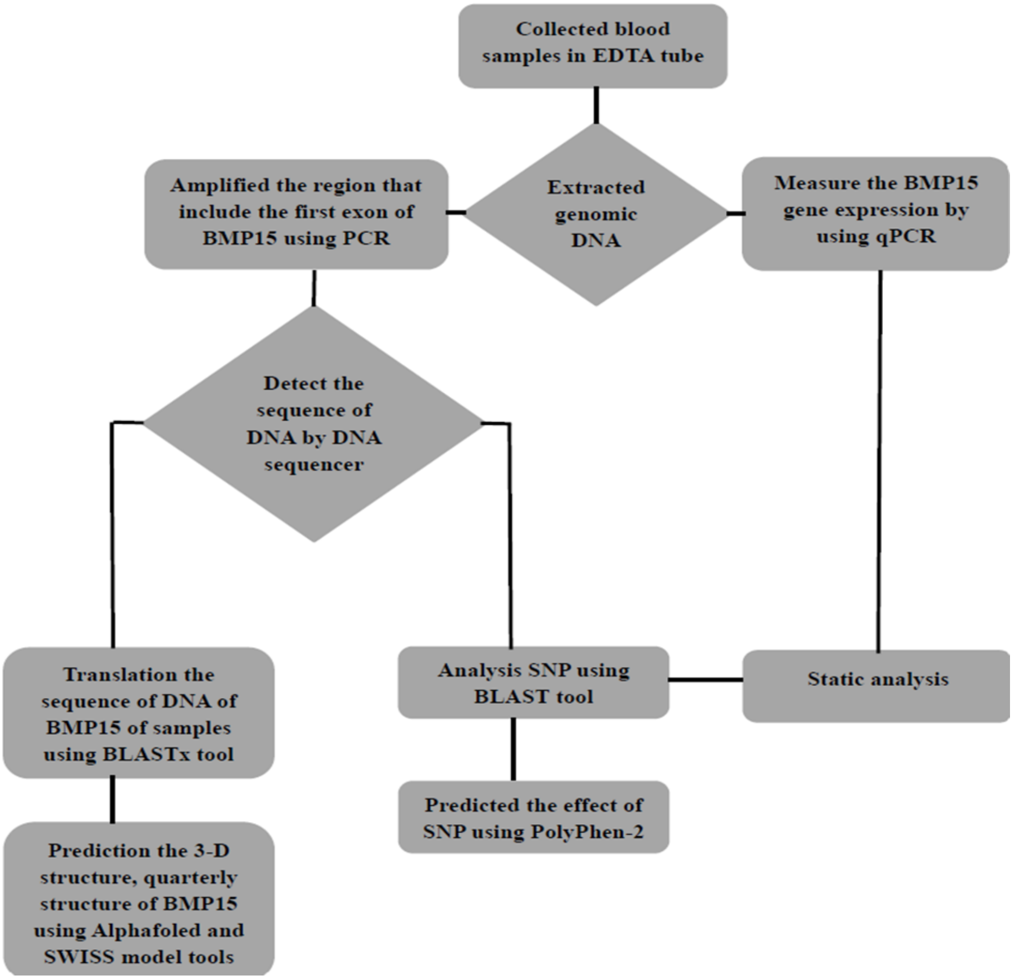


Figure 1. The flowchart represents the detailed procedure used to experiment. First, the blood samples were collected. Then, genomic DNA was extracted. Second, the BMP15 gene rs377085803 (BMP15 T/C) was detected. Third. DNA sequence was investigated. Finally, molecular docking and bioinformatics were used to study SNP polymorphism.

Patients and controls

The study aimed to predict future outcomes for both patients and control groups. It involved 100 women aged 25 to 45, categorised into two groups: one consisting of infertile participants diagnosed with polycystic ovary syndrome, and the other group comprising fertile women unaffected by the condition.

Primer design for the BMP15 gene

The gene-specific primers targeting the first exon of *BMP15* were designed based on the NCBI reference sequence, which is derived from the NCBI (Genome Database of the National Centre for Biotechnology Information): NC_000023.11. Gene-specific primers are also used for real-time PCR in *BMP15* gene expression analysis. The oligonucleotide sequence of the primers was synthesised and lyophilised by Bioneer Company,/Korea. **Table 1** displays all the oligonucleotide sequences of primers utilised in this study.

Table 1. Primers used in the present study.

Primer	Sequence (5′→3′ direction)	primer size bp	Product size bp	Tm °C
	BMP15 (Gene Expression)			
(Forward)	TGCAGATCCTGGAATCGCCT AGGTCCTCGGAATCACGTA	**20**	**125**	**62**
(Reverse)	ATGGTGCGGTTCTCTCTAGG	20	125	62
	GAPDH (Glyceraldehyde 3-phosphate dehydrogenase)			
Forward	AGCTTGACCTGACCATCTGGAAGA	24	160	58
Reverse	CTGAGGCTGGAAGAGGTAC	20	160	
	BMP15 (sequence)			
(Forward)	GTTGGGGCCTGTTGTTGAAC	20	414	59
(Revers)	TCCTCTCCACTTCTCTCCCT	20	414	

BMP15 gene rs377085803 (BMP15 T/C)

To target the SNP at rs377085803 (*BMP15* T/C) in the first exon region of the *BMP15* gene, a specific primer was developed. Primers were designed using a sequence template obtained from the NCBI (National Center for Biotechnology Information) database. Following synthesis, Alpha DNA Ltd (Canada) lyophilised the primers at-20°C. **Table 1** displays the sequences of all primers employed in the various allelic detection experiments.

Genomic DNA was extracted from blood samples using the EasyPure kit from TransGen Biotech (Beijing, China) (Cat. No: EE101-01). Following extraction, PCR was conducted. Following the manufacturer's instructions, the reaction mixture was prepared to a final volume of approximately 24 µl, consisting of 12.5 µl of 2xEasyTaq® PCR SuperMix (TransGen Biotech, China), 4 µl of DNA, 1 µl of each primer (10 mM), and 6.5 µl of nuclease-free water. The mixture was then placed in a thermocycler (Agilent, Germany), The programmed was set with the following optimized thermal cycling conditions: an initial denaturation at 94°C for 5 minutes (one cycle), followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds, conluding with a final extension at 72°C for 5 minutes (one cycle) [11].

DNA sequencing

To sequence the first Exon of the *BMP15* gene, Sanger sequencing was performed on amplified PCR fragments from 50 polycystic ovary syndrome and 50 standard samples employing an ABI3730XL automated DNA sequencer (Macrogen Corporation, Korea) [12]. After two weeks, the data were retrieved as a nucleotide sequence (in FASTA format).

Translation

The DNA sequence of the *BMP15* gene to an amino acid sequence employing the BLASTx server (https://blast.ncbi.nlm.nih.gov/Blast.cgi), translating DNA nucleotide to amino acids [13].

PolyPhen-2

To anticipate the functional impacts of amino acid replacement, use the protein variation effect analyser and Polymorphism Phenotyping v2 (http://genetics.bwh.harvard.edu/pph2). This tool employs a point system based on alignment [14].

Three-dimensionaland quarterly structure prediction

The AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/) is a sophisticated multicomponent artificial intelligence (AI) system that employs machine learning techniques to forecast the three-dimensional structure of a protein, utilising its primary amino acid sequence as input. By employing homology modelling techniques, the Swiss-Model (http://swiss-model.expasy.org/) can anticipate the three-dimensional structure of proteins encoded from the first exon of the *BMP15* gene [13, 15].

Gene expression of BMP15

After total RNA was isolated, the expression of the *BMP15* gene was measured employing the reverse transcription-quantitative polymerase chain reaction (RTqPCR) technique [16]. Instructions provided by the manufacturer were followed when employing the commercially available reagent [17] (Trizo, Trans; India) to isolate the total RNA. Total RNA was reverse-transcribed into complementary DNA using the EasyScript® One-Step gDNA Removal and cDNA Synthesis SuperMix Kit (cDNA). The procedure was performed in a 20µl reaction volume, as recommended by the manufacturer. Twenty microliters of total RNA were needed for reverse transcription. CDNA was used as a template. The RT-qPCR was performed with TransStart® Top Green qPCR Super Mix (TransGen Biotech, Cat. Trachemys scripta elegans (ALCBUL, Ahrensburger Lohe bei Buchholz Nr. 1, No: AQ131-01) [18]. Reference sequences for *BMP15* (forward and reverse oligonucleotides), along with the primers of the housekeeping gene *GAPDH* [19]. The reaction mixture was prepared to a final volume of 20 µl according to the manufacturer's instructions. Each reaction contained 10 µl of 2X TransStart® Top Green qPCR Super Mix for (probes) or SuperMix UDG without Rox Dye II (for SYBR-green). ROX Dye II is either absent or present at a lower concentration compared to standard kits, minimising its interference with reaction dynamics and internal reference signals. Primers were added at the following final concentrations: Forward primers targeting Exon1–800 nM and reverse primers targeting intron sequences at approximately 600 µM µm. This assessment aimed to produce a more consistent CT value with industrial process conditions compared to conventional multi-exon approaches. RNase-Free Water was added to bring the final volume to 12.5 µL in some instances or up to 20 µL in others, depending on special experimental modifications. Following this, the mixture was subsequently subjected to the optimized cycling conditions in a real-time thermocycler (MIC-4, MX 3000P™ / Stratagene, USA): initial denaturation at 94°C for 30 seconds, Denaturation step at 95ºC for the annealing step; the extension step was followed by a single melt curve cycle to verify amplification specificity. Gene expression fold change was calculated as the fold difference in target gene expression relative to an endogenous housekeeping gene, with normalisation based on the CT value obtained from control samples [20].

Ethics approval and consent to participate

All the protocols used in these experiments were approved by the Human Care and Ethics Committee, College of Applied Sciences, University of Technology—Iraq (Ref. No. 12/CAS/2023). All methods were carried out in accordance with the Guidelines of the U.S. National Institutes of Health (NIH Publication No. 86–23, Revised 1996). Informed consent was obtained from all subjects and/ or their legal guardian.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics 26 to evaluate the impact of various factors on the study parameters. The significance of differences between means was assessed using one-way ANOVA and the T-test. Results are presented as mean ± standard deviation. Categorical variables were analysed with the Chi-square test to compare percentages, with significance levels set at 0.05 and 0.01. The Chi-square test was also applied to compare the frequencies of genotypes and allelic variants between patient and control groups [21, 22]. In addition, the distribution of the genotype of the rs377085803 polymorphism in the control group was tested for Hardy-Weinberg equilibrium (HWE) to assess whether the observed genotype frequencies were consistent with those expected under random mating conditions. Allele frequencies were calculated from observed genotype counts, and expected genotype frequencies were determined using the Hardy-Weinberg equation ($p^2 + 2pq + q^2 = 1$), where p represents the frequency of the T allele, and q represents the frequency of the C allele. The goodness of fit between observed and expected genotype distribution was assessed using the chi-seguare(x^2) test. A p-value greater than 0.05 was considered indicative of conformity with the Hardy-Weinberg equilibrium.

Results and Discussion

PCR

In the present study, PCR was employed to amplify the first exon of the *BMP15* gene using DNA isolated from patients' blood and controls. Three primers, including Forward and Reverse primers for *BMP15*, were designed by the primer3 software and synthesised by Bioneer Company (Korea). The primer (*BMP15* F and R) successfully amplified a 414 base pair fragment, which was visible as a distinct band following electrophoresis on a 2% agarose gel run at 60 volts for 90 minutes. A total of 100 DNA samples were analysed, as shown in **Figure 2**.

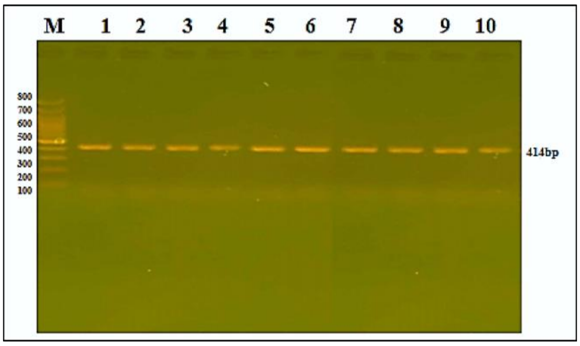


Figure 2. *BMP15* gene PCR product (first exon) of 414 bp molecular size. Electrophoresis was applied with ethidium bromide on a 2% agarose gel at 60 volts for 90 minutes. Lane M: DNA ladder (100-800 bp). Lane (1-5): First exon products for the Healthy control group. Lanes (6-10): First exon products for PCOS.

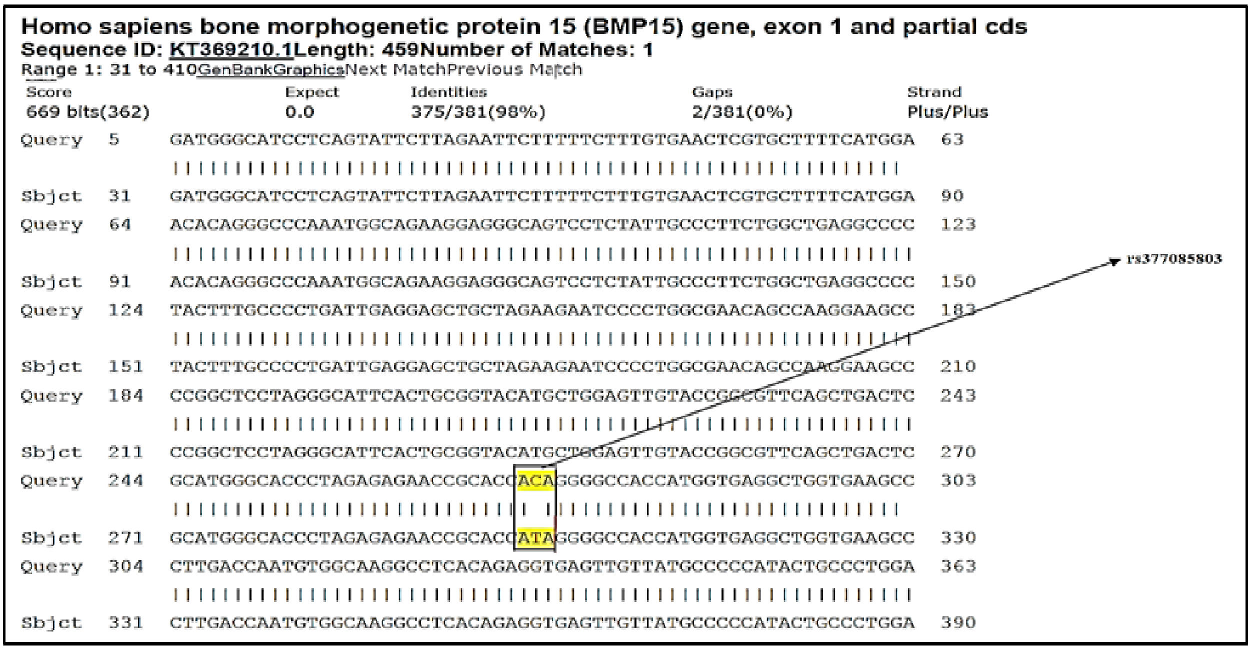
Sequencing of the BMP15 gene

In this study, direct sequencing was performed using forward primers on patient samples, displaying the chromatogram for the forward nucleotide sequence from a PCR product amplified for a patient with PCOS. Genotype analysis of the *BMP15* gene for the primer's PCR product indicated genetic alteration [23]. This alteration, identified as a single-nucleotide polymorphism, resulted in a missense mutation affecting the translation process.

The SNP (rs377085803 T/C)of BMP15 gene

The SNP of the *BMP15* gene (rs377085803T/C; located on Chromosome X: 50911052 bp) was presented with three genotypes (TT, TC, and CC) and two alleles (C and T). The study demonstrated that the frequency of Rs377085803 polymorphism in the patient group was more statistically significant ($p < 0.01$) than that in healthy fertile women (control). The genotype distribution of the rs377085803 polymorphism in the BMP15 gene differed markedly between the PCOS patients and the healthy control group. In the PCOS group (n=50), the homozygous TT genotype was observed in 2 women(4.0%), while the heterozygous TC genotype was detected in 48 women

(96.0%). While the CC genotype was not observed in either group. In contrast, the control group (n=50) displayed a predominance of the TT genotype, which was detected in 47 women (94.0%), whereas the TC genotype was observed only in 3 women (6.0%). The differences in genotype distribution between PCOS patients and controls were statistically significant ($\chi 2=77.47$, $P<0.0001$). Regarding allele distribution, the frequency of the T allele in the PCOS group was 0.52, while the C allele frequency was 0.48. In the control group, the Tallel frequency was 0.97, whereas the C allele frequency was 0.03. These findings indicate a significantly higher frequency of the allele among PCOS patients compared with healthy controls. The results suggest that the heterozygous TC genotype of rs377085803 may be associated with an increased risk of PCOS, whereas the TT genotype appears to be more prevalent in healthy fertile women and may therefore represent a protective genotype. The sequence analysis using the NCBI BLASTn tool confirmed the presence of a T-to-C nucleotide substitution in the coding region of the BMP15 gene. Because this single nucleotide variant (SNV) occurs within an exon, it leads to a missense mutation resulting in an amino acid substitution (Ile90Thr) in the BMP15 protein. This mutated nucleotide was identified using NCBI (BLASTn) and is reported for the first time in Iraqi patients. As the SNV is located in an exon, nucleotide translation to protein is demonstrated in **Figure 3**.



```
Homo sapiens bone morphogenetic protein 15 (BMP15) gene, exon 1 and partial cds
Sequence ID: KT369210.1Length: 459Number of Matches: 1
Range 1: 31 to 410GenBankGraphicsNext MatchPrevious Match
 Score                   Expect      Identities              Gaps              Strand
 669 bits(362)           0.0         375/381(98%)            2/381(0%)         Plus/Plus
Query  5     GATGGGCATCCTCAGTATTCTTAGAATTCTTTTTCTTTGTGAACTCGTGCTTTTCATGGA  63
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  31    GATGGGCATCCTCAGTATTCTTAGAATTCTTTTTCTTTGTGAACTCGTGCTTTTCATGGA  90
Query  64    ACACAGGGCCCAAATGGCAGAAGGAGGGCAGTCCTCTATTGCCCTTCTGGCTGAGGCCCC  123
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  91    ACACAGGGCCCAAATGGCAGAAGGAGGGCAGTCCTCTATTGCCCTTCTGGCTGAGGCCCC  150
Query  124   TACTTTGCCCCTGATTGAGGAGCTGCTAGAAGAATCCCCTGGCGAACAGCCAAGGAAGCC  183
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  151   TACTTTGCCCCTGATTGAGGAGCTGCTAGAAGAATCCCCTGGCGAACAGCCAAGGAAGCC  210
Query  184   CCGGCTCCTAGGGCATTCACTGCGGTACATGCTGGAGTTGTACCGGCGTTCAGCTGACTC  243
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  211   CCGGCTCCTAGGGCATTCACTGCGGTACATGCTGGAGTTGTACCGGCGTTCAGCTGACTC  270
Query  244   GCATGGGCACCCTAGAGAGAACCGCACCACAGGGCCACCATGGTGAGGCTGGTGAAGCC  303
             |||||||||||||||||||||||||||| | |||||||||||||||||||||||||||
Sbjct  271   GCATGGGCACCCTAGAGAGAACCGCACCATAGGGCCACCATGGTGAGGCTGGTGAAGCC  330
Query  304   CTTGACCAATGTGGCAAGGCCTCACAGAGGTGAGTTGTTATGCCCCCATACTGCCCTGGA  363
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  331   CTTGACCAATGTGGCAAGGCCTCACAGAGGTGAGTTGTTATGCCCCCATACTGCCCTGGA  390
```

Figure 3. Alignment of exon one and its polypeptide product; BLASTn results for exon 1 showing 99% identity, T replaced with (C) at position 273.

Which translated the sequence of DNA to their corresponding amino acid sequences with the aid of the online program EXPASY translate tool [23]. That gives the amino acid sequence for each codon, then the following translation is the alignment of the peptide sequence by the aid of BLASTp (the protein alignment tool) that helps to detect the SNV impact on the amino acid sequence in the polypeptide.

The Hardy-Weinberg equilibrium

The genotype distribution of the rs377085803 polymorphism in the control group was tested for Hardy-Weinberg equilibrium. The calculated allele frequencies were 0.97 for the T allele and 0.03 for the C allele. Based on these frequencies, the expected genotype counts were 47.04 for TT, 2.91 for TC, and 0.05 for CC. Comparison between the observed and expected genotype frequencies using the chi-square test showed no significant deviation from Hardy-Weinberg equilibrium ($X2=0.048, p> 0.05$). These results indicate that the control population was genetically stable and suitable for subsequent association analysis.

Predicted the pathogenesis of SNP:rs377085803 I/T by PolyPhen-2

The first exon of the *BMP15* gene normally contains the codon ATT, which codes for the amino acid isoleucine (Ile) at position 90. In infertile women, with the rs377085803 single-nucleotide polymorphism (SNP), this code is altered to ACT instead of ATT, resulting in substitution of the threonine (Thr) at the same position. However, this SNP affected the structure of the *BMP15* protein.

The SNP resulting in an isoleucine-to-threonine substitution at position 90 (rs377085803) in the BMP15 gene received PolyPhyn-2 a score of 0.455; therefore, this mutation is predicted to be possibly damaging. This prediction is supported by a sensitivity of 0.455 and a specificity of 0.81.

Structure analysis of bone morphogenetic protein-15

The *BMP15* gene encodes bone morphogenetic protein-15, which consists of a single chain A of 394 amino acids that includes a signal peptide at position 1 to 18, a large pro-region (**PRO-0000244399**) at position 19 to 2649, and a mature peptide(**PRO-0000244400**) at position 267 to 394.

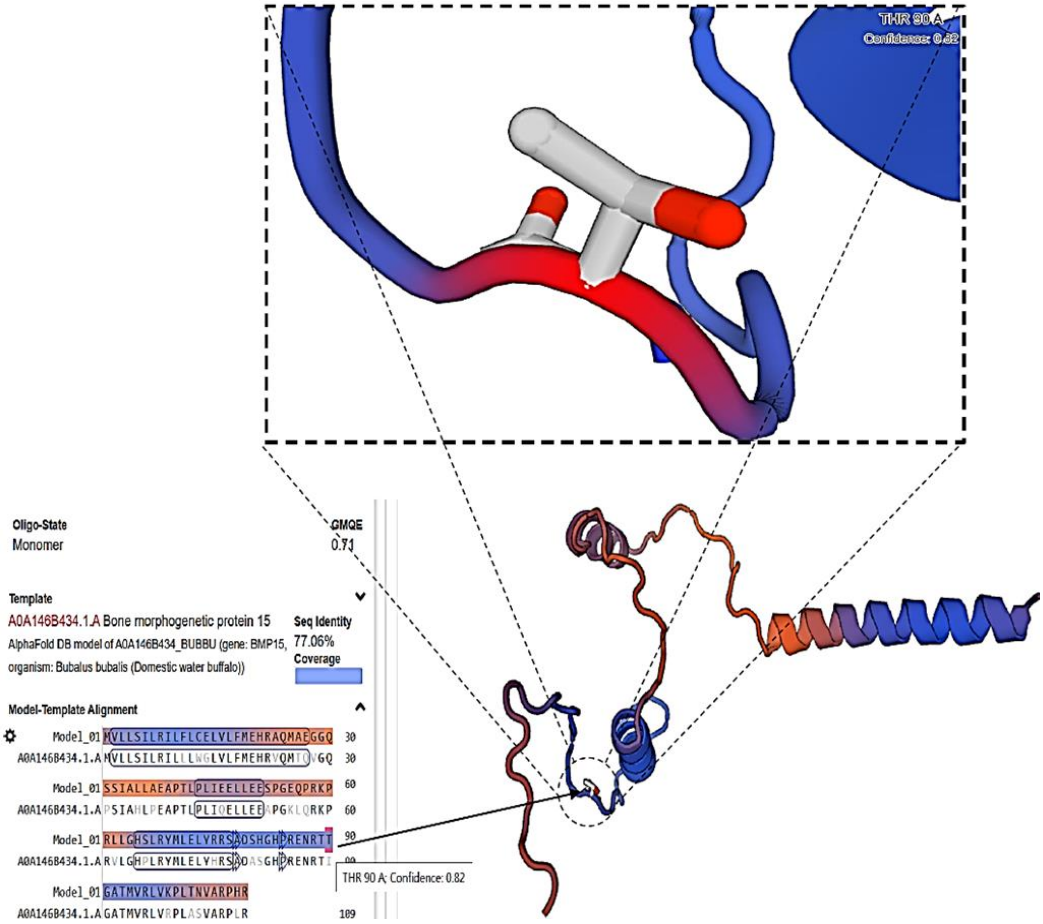
The post-translational modifications, including the N-linked glycosylation of asparagine at positions 87,238 and 375, are a complex and vital process that influences protein structure and function. The implications of this modification can be paramount in both physiological and pathological contexts, and its study can contribute significantly to our understanding of protein chemistry and biology.

Predict position of the SNP: rs377085803 on the structure of first exon of BMP15 protein

BMP15 is a member of the TGF-β superfamily, primarily expressed in the ovaries, and plays an essential role in folliculogenesis and oocyte maturation [24]. The three-dimensional structure was predicted using the AlphaFold and SWISS-MODEL tools, indicating threonine (Thr) amino acids at position 90, which region is encoded by the first exon of *BMP15*, which forms the signal peptide and a large pro-region of protein *BMP15*.

The pro-region of *BMP15* is a precursor sequence that is often cleaved off to activate the protein. This pro-region can contain structural features, such as bends or beta turns, which might be critical for correct folding and subsequent signalling activity [25]. SNP: rs377085803, located at a bend or beta turn of the pro-region of *BMP15*, can significantly influence the protein's structure and function, leading to potential reproductive health consequences. Understanding these SNPs is crucial for developing effective diagnostic and therapeutic strategies in reproductive medicine.

The SNP rs377085803, which causes a substitution of isoleucine (Ile) with threonine (Thr) at position 90, has been associated with disrupted protein folding as illustrated in **Figure 4**. This alteration in protein structure is linked to the pathogenic effect of the mutation. The study highlights a significant correlation between genetic variation and women's infertility related to PCOS.



Oligo-State
Monomer

GMQE
0.71

Template
A0A146B434.1.A Bone morphogenetic protein 15
AlphaFold DB model of A0A146B434_BUBBU (gene: BMP15, organism: Bubalus bubalis (Domestic water buffalo))

Seq Identity
77.06%

Coverage

Model-Template Alignment

```
Model_01         MVLLSILRILFLCELVLFMEHRAQMAEGGQ 30
A0A146B434.1.A   MVLLSILRILLLWGLVLFMEHRVQMTQVGQ 30

Model_01         SSIALLAEAPTLPLIEELLEESPGEQPRKP 60
A0A146B434.1.A   PSIAHLPEAPTLPLIQELLEEAPGKLQRKP 60

Model_01         RLLGHSLRYMLELYRRSADSHGHPRENRTT 90
A0A146B434.1.A   RVLGHPLRYMLELYHRSADASGHPRENRTI 90

Model_01         GATMVRLVKPLTNVARPHR
A0A146B434.1.A   GATMVRLVRPLASVARPLR            109
```

Figure 4. The three-dimensional structure prediction for the amino acid sequence of exon 1 of the *BMP15* protein shows SNP: rs377085803 that changes the threonine (The) to isoleucine (ILE) at position 90, with confidence 0.82 by the AlphaFold tool.

SWISS-MODEL identified 50 potential templates for the target sequence, with template Q6PX77.1. A (Bone morphogenetic protein 15) showing the highest relevance. This template exhibited 1.00% query coverage and 74.68% sequence identity, along with a 0.53% sequence similarity. The GMQE (Global Model Quality Estimation) score for this template was 0.71, indicating a reliable prediction model for the protein structure. Analysis of the Ramachandran plot for φ and ψ angles in the AF-Q6PX77-F1-model_v4 revealed that 99.7% of the residues were situated in the favoured region, and 95.0% were within allowed regions, while only 80.0% were found in the outlier region. In addition to these Ramachandran outliers, the protein exhibited rotamer outliers at approximately 2.82%. The chain contained a total of 31 bad angles. Overall, the Ramachandran plot analysis indicates that the protein's torsional angles are well-positioned, suggesting that the structure is highly reliable [66-70].

In AF-Q6PX77-F1-model_v4, the Ramachandran plot analysis of φ and ψ angles for infertile women with PCOS that contain SNP rs377085803, the amino acid residues revealed that only 80.0% of the residues were located in the outlier region, while 99.7% of the residues were within the preferred and 95.0% in the allowed zones. The protein also exhibited 1.99% rotamer outliers and 2.82% Ramachandran outliers, with a total of 31 unfavourable torsion angles in the chain. Although some residues occupy acceptable regions, the presence of multiple outliers suggests that the protein's torsional geometry is compromised, indicating that the overall structure may not be entirely reliable.

Domain analysis of protein BMP15

Domain information regarding protein *BMP15* was obtained using the InterProScan database. The 394-amino acid sequence of *BMP15* was initially analysed against a non-redundant protein sequence database. To gain additional insight into the protein's function, the sequence was further examined using a secondary database, which identified associated functions, families, or domains. The InterPro and Panther databases identified *BMP15* as part of the transforming growth factor-beta-related (TGF-beta-related) and *BMP15* protein families. Specifically, InterPro assigned it to the TGF-beta-rel (IPR015615) and BMP-15 (IPR015923) families, while Panther classified it under the TGF-BETA family (PTHR11848) and a subfamily of bone morphogenetic proteins (PTHR11848:SF22). The amino acid position for protein families was predicted from 5 to 392 amino acids [61-66]. The domain prediction of protein *BMP15* was performed by InterPro domain, Prosite profiles, Pfam, and SMART databases. InterPro domain (IPR001839) and Prosite profiles (PS51362) predicted domain sites from 264-392 amino acids. Whereas, Pfam (PF00019) identified the domain region of protein *BMP15* starting from 290 to 392. On the other hand, SMART (SM00204) predicted the domain region from 291 to 392. The homologous superfamily for protein *BMP15* was predicted by three databases: InterPro homologous superfamily (IPR029034), SUPERFAMILY(SSF57501), and CATH-Gene3d (G3DSA:2.10.90.10) at sites 277-392, 284-392, and 277-392, respectively. The conserved site was identified by InterPro conserved sites (IPR017948) and PROSITE patterns (PS00250) between regions 309 and 324. Gene Ontology (GO) analysis predicted several functional attributes of *BMP15*, including its involvement in biological processes such as granulosa cell development (GO:0060016) and ovary follicle development (GO:0001541).

The molecular function of BMP15 was associated with growth factor activity (GO:0008083), and its cellular component was predicted to be in the extracellular space (GO:0005615) **(Figure 5)**.

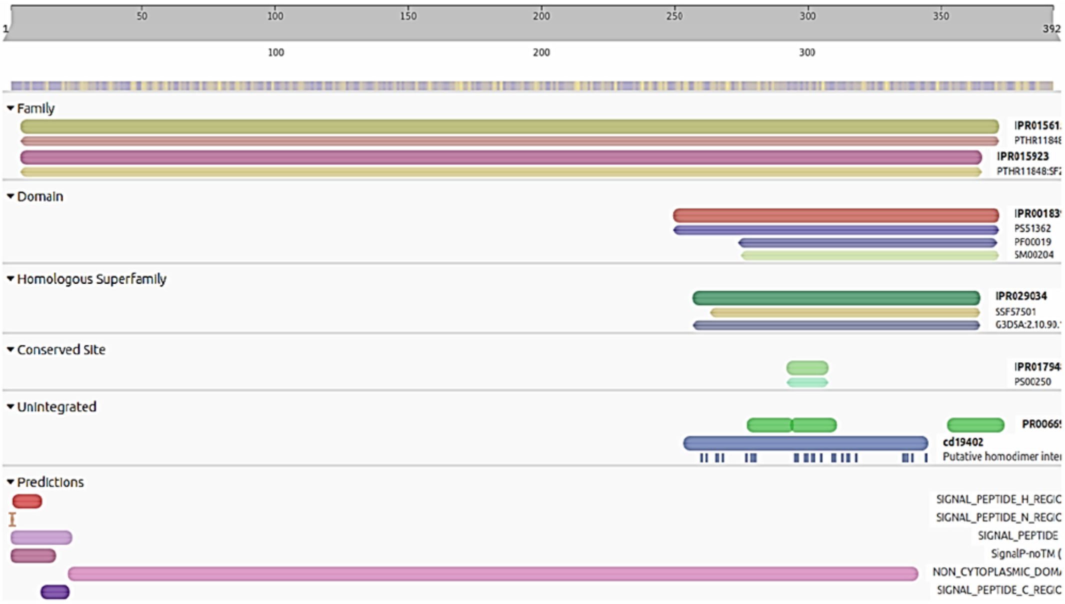


Figure 5. Domain information regarding protein *BMP15* was inferred from the InterProScan database.

BMP15 gene expression

Quantitative expression analysis of the BMP15 gene was conducted using reverse transcription-quantitative polymerase chain reaction (RT-qPCR), allowing for the measurement of relative gene expression levels. The gene expression was normalised to a housekeeping gene (GAPDH) level and quantified by the ΔCt value and folding ($2^{-\Delta\Delta ct}$) method. **Table 2** reveals a highly significant difference in ΔCt values (p = 0.0001**) between the fertile control group (6.725 ± 0.18) and the polycystic ovary syndrome (PCOS) group (6.312 ± 1.17).

The fold expression level of the BMP15 gene in the PCOS group was notably reduced (0.507) compared to the control group (1.000), indicating a downregulation of BMP15 gene expression in individuals with PCOS. These findings imply that the mean of $2^{-\Delta Ct}$ differed significantly among these groups (p=0.001**). It was found that *BMP15* gene expression was down-regulated in PCOS patients, which corroborated previous reports that low *BMP15* levels contributed to female infertility.

Table 2. The expression level of the *BMP15* gene in samples of healthy fertile females (controls) and PCOS infertile females.

Study Groups	Mean ± SD of				Fold of *BMP15* gene expression
	BMP15 Ct value	ΔCT	ΔCTC	ΔΔCT	$2^{-\Delta Ct}$
Group 1: healthy	23.651± 1.03	6.725± 0.18	5.041± 0.83	1.683± 0.77	1.000
Group 2: (PCOS)	24.334± 1.11	6.312± 1.17	5.204± 0.67	1.101± 1.13	0.507
P-value	0.0001**	0.0001**	0.0001**	0.005**	0.001**

The current study revealed that the original mRNAs were found in the samples. Moreover, the patients' group is correlated with a reduced copy number of mRNAs, suggesting that the gene expression of the *BMP15* gene is decreased in the study group (PCOS) compared to the control group. These findings demonstrate that *BMP15* gene expression is reduced in the patient group, implying that the *BMP15* gene could be used as a biomarker for early infertility diagnosis [26]. Numerous studies have targeted *BMP15*, showing that it is essential to folliculogenesis, oocyte maturation, and ovulation.

The bone morphogenetic proteins (BMP) family, particularly the 15 (*BMP15*) gene, is significantly involved in regulating follicle development and ovulation [27]. A single-nucleotide polymorphism (SNP), rs377085803, located in the first exon of the *BMP15* coding region, has the potential to alter the protein's structure [54-60]. This genetic variant has been examined in previous association studies for its influence on reproductive traits [28]. The present study aimed to identify the role of polymorphism in the risk of female infertility within the context of the meta-analysis. The *BMP15* polymorphism (rs377085803) is on the gene sequence encoding the pro-region of the *BMP15* protein, which is critical for its processing and dimerisation in prior research [28]. The rs377085803 (T>C) is located at base 273 in the reference gene (ID: KT369210.1). A single-nucleotide variant (SNV) in this exon was shown to affect the resulting polypeptide by altering the codon from ATT, which encodes for isoleucine, to ACT, which encodes for threonine. The three-dimensional structure of the first exon was predicted using the SWISS model tool, indicating positions of isoleucine (Ile) that change with threonine (Thr) amino acids at position 90. This structural alteration shows the SNP's potential impact on protein folding, consequently affecting overall protein structure [29]. This SNP showed a significant association with infertility cases due to PCOS in comparison to the control group. In summary, the data published before 2014 showed that approximately 4.5% of women with PCOS-related infertility carried *BMP15* genetic variants, compared to only about 0.43 % among women with normal ovarian function [30]. Mutations in this gene are linked to ovarian dysgenesis and have been associated with polycystic ovary syndrome. Disruptions in the *BMP15* gene sequence can interfere with folliculogenesis, potentially leading to infertility in women [31]. The current study emphasises the vital role of *BMP15* in maintaining ovarian function. *BMP15* is closely linked to reproduction and various female reproductive disorders. This protein, which is secreted by oocytes, plays a key role in regulating their maturation and female fertility [32]. Similarly, transforming growth factor β (TGF-β), which is also produced in the female gonad, exhibited comparable functions to those of *BMP15*[33]. In mammals that typically release a single egg per ovulation, such as humans, *BMP15* is essential in regulating follicular development and ovulation rate in fertile women [34]; the lower level of *BMP15* expression is associated with subfertility, damage to ovulation, and even ovarian failure in women [35]. Several studies have paid attention to the infertility phenotypes based on follicular development [36], with findings showing that *BMP15* gene expression was reduced in the infertile females but increased in the fertile, healthy females [37]. Several studies have contributed to understanding the general mechanisms of ovarian folliculogenesis in humans, highlighting a complex hormonal interaction involving the central nervous system, pituitary, and ovary, coordinated by various intraovarian paracrine signalling [38]. Some differentially expressed genes, including *BMP15*, a member of the transforming growth factor beta (TGFbeta) superfamily, are specifically expressed in oocytes [43-53]. Functionally, *BMP15* interacts with two types of transmembrane serine/threonine kinase receptors, triggering paracrine signalling that significantly promotes ovarian granulosa cell growth and proliferation [39]. This protein is crucial in regulating oocyte development competence and determining ovulation rates. Remarkably, mutations in the *BMP15* gene are associated with different ovarian phenotypic abnormalities. The phenotypic effects of BMP15 gene alterations vary across species, ranging from sterility to increased fertility, and from mild subfertility to complete infertility in females. In women, these changes are linked to conditions such as primary ovarian insufficiency (POI) and polycystic ovary syndrome [40]. In particular, gene expression profiling has revealed a strong association between *BMP15*, ovarian folliculogenesis, and infertility [41]. Overexpression of a biologically active *BMP15* accelerates folliculogenesis and is strongly associated with improved fertilisation rates and embryo quality [42]. In contrast, *BMP15* expression is reduced in infertile women, particularly with polycystic ovary syndrome. This study shows that *BMP15* is down-regulated in women with PCOS, and genetic variations, such as SNPS, may lead to structural defects in the protein, consequently impairing normal protein expression and function.

Conclusion

In conclusion, *BMP15* expression was significantly reduced in Iraqi women with PCOS compared with healthy controls. In addition, the rs377085803 (T>C) variant, which results in an Ile90Thr substitution in exon 1 of *BMP15*, showed a significant difference in genotype distribution between the two groups. In silico analysis suggested that this substitution may influence the local structure of the *BMP15* pro-region. These findings support a possible association between *BMP15* alterations and PCOS in this cohort. However, the relatively small sample size and the lack of functional validation mean that larger studies are needed before the variant can be considered a reliable biomarker or causal factor.

Study limitation

This study has several limitations. First, the sample size was relatively small and restricted to a single population, which may limit the generalizability of the findings. Second, BMP15 expression was measured in peripheral blood rather than ovarian tissue or granulosa cells, and therefore may not fully reflect ovarian gene activity. Third, the predicted structural effect of rs377085803 was based on in silico tools and was not validated experimentally. Finally, larger multicentre studies with functional assays are required to confirm the association between this variant and PCOS.

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