

Association of Wnt4 (rs121908652) and Bmp15 (rs104894766) polymorphisms with endometriosis risk in Iranian women

Shima Rezaei Afarjani

Islamic Azad University

Seyed Mehrdad Kassaee

Kassaee2001@iauh.ac.ir

Islamic Azad University

Article

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Abstract

Endometriosis is a multifactorial and polygenic disorder with a strong genetic aspect in endometrium characterized by the presence of endometrial tissue outside the uterine cavity. This disorder is associated with pelvic pain and infertility in women. The present work aimed at investigating the association between the risk of endometriosis in Iranian women and the polymorphisms in *BMP15* rs104894766 and *WNT4* rs121908652. In the present case-control study, the variants were investigated in 100 patient women with endometriosis and 100 healthy subjects (both groups aged 20–35 years old) using PCR-RFLP methods. Statistical analysis was performed with SPSS software using the χ^2 test and calculation of the odds ratios (OR) at 95% confidence intervals. There was significant association between the risk of endometriosis and the *Wnt4* rs12190865 polymorphism ($p = 0.02$, OR = 0.5) at genotypic and allele levels. No significant association was observed between endometriosis and the *BMP15* rs104894766 polymorphism ($p = 0.2$, OR = 0.72). The polymorphisms in the *Wnt4* gene might be related to the pathogenesis of endometriosis in infertile adult women.

Introduction

Endometriosis is a common gynecologic disease, affecting almost 10% of women in reproductive age ¹. It is defined by the presence of endometrial glands and stroma outside the uterus ². The tissue may frequently develop on the ovarian surface, behind the uterus, in the pelvic cavity, on the intestinal wall, and in other sites including the peritoneum, the uterosacral ligaments, the fallopian tubes, the uterine surface, and the rectovaginal septum. Less frequently, lesions may involve cesarean-section or surgical scars, the bladder, the diaphragm, and more distant sites such as the brain or extremities ³. The ovary is the most frequent site of endometriosis, and both ovaries are involved in approximately 50% of cases ⁴.

Endometriosis is classified into four stages—minimal, mild, moderate, and severe—reflecting the location and severity of the lesions. Symptoms may depend on the location of active endometriosis, although this is not always the case; the most common manifestations are pelvic pain and infertility ^{5,6}. The disorder can occur at any age from puberty to menopause but is most frequently observed between 20 and 40 years old ⁷, typically during the reproductive cycles ⁷. The symptoms are often exacerbated with the menstrual cycle ⁷ because the ectopic endometriotic tissue exhibits a comparable hormonal changes and responses to those of intrauterine endometrial cells. The normal endometrium lining the uterus responds to cyclic changes in female hormones.

The overall prevalence of endometriosis is not precisely known and varies according to geographic location and ethnicity ³. Prevalence is estimated at approximately 10–30% in infertile women and lower in fertile women ⁷. Endometriosis is a common finding in infertile women because the site of the disease depends on the route of endometrial-tissue transfer, and because retrograde menstruation is the most common mechanism ⁸.

Endometriosis was recognized as a multifactorial and polygenic disorder with a strong genetic component⁹. The role of immediate relatives was one of the first genetic factors confirmed by extensive investigations¹⁰. Women whose mothers or sisters have endometriosis have a 6- to 9-fold higher risk of developing the disease¹⁰. The disease is commonly observed in both monozygotic and dizygotic twins and begins at similar ages in non-twin affected sisters. Prevalence among immediate relatives of affected women is 6- to 7-fold higher than the general population¹¹. These observations indicate that endometriosis has a genetic basis and that susceptibility is inherited as a complex genetic trait. Several genes were recognized to play a role in the development of endometriosis¹⁰.

Identification of the genes and chromosomal regions involved in endometriosis is therefore of great importance for understanding its pathophysiology, identifying individuals at risk, and enabling appropriate treatment. The previous research works has shown a significant relationship between genes involved with fertility and endometriosis⁶. Many infertile women may have endometriosis, yet the underlying cause is often not readily apparent; the relationship between infertility and endometriosis remains incompletely understood. It is possible that endometriotic lesions secrete factors that are detrimental to gametes or embryos. Endometriosis may cause miscarriage in women and may affect fertility either directly or through secondary mechanisms. Infertility associated with endometriosis is therefore of considerable clinical importance⁸. Among the genes involved in cellular and physiological processes in fertility, the *Wnt* and *Bmp* gene families are particularly important¹². The *Wnt4* has a clear impact on fertility in both genders, especially in females. The literature data indicate a wide range of studies regarding the association of *Wnt4* gene family with fertility and mechanisms of ovulation worldwide. These investigations demonstrate the association of polymorphisms and similar mutations with fertility^{13,14}. The role of *Wnt* gene family, particularly *Wnt4*, in regulating and evolving the reproductive system and cellular mechanisms of ovulation were well established^{15,16}.

Bone morphogenetic proteins (BMPs) are secreted signaling molecules belonging to the transforming growth factor- β (TGF- β) superfamily. More than 30 members of this family had been identified till now¹⁷. These growth-factor molecules act primarily at epithelial–mesenchymal sites and in interactions between them. When their expression was examined by mutation or genetic alteration, a wide range of functions in the development of the skeletal, nervous, and hematopoietic systems was revealed¹⁸. The BMP signals act on non-hematopoietic cells and promote cell survival. The BMPs regulate the development and function of tissues¹⁹ and play regulatory roles in various cellular processes, including proliferation, differentiation, and apoptosis²⁰. The *BMP15* gene is located on the X chromosome and comprises two exons separated by a 4.5-kb intron. Its complete transcript is a 1179-nucleotide sequence encoding a 393-amino-acid prepro-peptide; the mature peptide is 125 amino acids long. Examination of mutations in this gene has shown that even a single amino-acid substitution can exert marked effects and that the smallest change can significantly influence ovulation rate²¹.

Given the importance of the *Wnt4* and *BMP15* genes in tissue formation and embryonic survival, it is critical to find the association of the polymorphism in the *Wnt4* rs121908652 and *BMP15* rs104894766

with susceptibility to endometriosis. The polymorphisms on these genes have been studied in different parts of the world, and it was shown that the overall prevalence of endometriosis depends on geographical location and race as well ²². To the best of our knowledge, this is the first report on the association of two genetic variants on endometriosis in Iranian women. Considering the genetic diversity of the Iranian population and the specificity of the polymorphisms of each race, it is important to investigate the endometriosis polymorphisms in this population. Previously, there were investigations on the association between endometriosis and healthy diet ²³ as well as between genetic mutations and infertility among Iranian women ²⁴. The identification of genetic variants as diagnostic and predictive factors for managing reproductive and childbirth healthcare is essential and should be conducted in Iran. Therefore, this research work aimed at investigating the frequency of polymorphisms in the *BMP15* and *Wnt4* genes and their association with the risk of endometriosis in Iranian women.

Materials and Methods

Patient population and study design

This case-control study was conducted on 100 women with a history of endometriosis of unknown etiology who attended the gynecology center of Tehran Women Hospital, Iran, who had no hormonal, anatomical, or genetic disorders (case group), and on 100 fertile healthy women with at least one child and no signs or symptoms of miscarriage or endometriosis (control group).

The patient and control groups were selected from the same ethnic area. The screening process involved initial evaluation by a gynecologist, diagnosis and confirmation of the diseases, data collection through a research questionnaire and in-person interviews. Due to the novelty of the examination of the targeted polymorphisms, the allele frequency was not known in the Iranian population. The participants of both groups were nearly age matched.

Materials

The chemicals including isopropanol, ethanol, KCl, EDTA, boric acid, and $MgCl_2$ were bought from Merck (Darmstadt Germany) in analytical reagent grade. The Tris hydrochloride was purchased from Sigma-Aldrich (Darmstadt, Germany) in molecular biology grade. The double distilled water purchased from Ghatran Shimi (Tehran, Iran).

Genotyping

After obtaining informed consent from both patient and healthy subjects, 5 mL of blood was collected into EDTA-containing tubes. DNA was extracted using a commercial kit (GenID, Strasberg, Germany) according to the instructions of the manufacturer. The samples from each participant were diluted with water to reach the DNA concentration of 50 ng/ μ L for further molecular assays. To this end, the optical

density (OD) of the specimens were read using a NanoDrop Microvolume Spectrophotometer (Thermo Fisher Scientific Inc., Singapore). The DNA hydration solution of each participant (50 µL) was then kept at -20 °C. The DNA samples were stored at -20°C until use.

Genotyping was performed by polymerase chain reaction–restriction-fragment-length polymorphism (PCR-RFLP). The PCR reaction mixture (final volume 25 µL) contained 2 µL of each forward and reverse primer, 3 µL of extracted DNA, 12.5 µL of master mix (GenID, Germany), and sterile distilled water to volume. PCR amplification of the target gene was carried out with primers designed using Gene Runner software. Primers were designed according to a Primer Blast program at NCBI and checked by Gene Runner software.

The primer sequences of *BMP15* were: Forward: 5'-AACTGGTCCTTTTCATGGAACACA-3'; Reverse: 5'-ATATTCCTCGGTTTGGTCTGAGAG-3'. The sequence of primers for *Wnt4* was 5'-GTCAGTGGGGAGCATCTCAG – 3' as forward primer, and 5'-CACACCTGCCGAAGAGATGG – 3' as reverse primer.

Amplification was performed on a thermocycler (Eppendorf, Germany) under the following conditions for the genes.

Wnt4

1 cycle denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 40 s, annealing at 60°C for 45 s, and extension at 72°C for 40 s, and finally one cycle of final extension at 72°C for 5 min

BMP15

initial denaturation at 94°C for 5 min; 35 cycles of denaturation at 94°C for 45 s, annealing at 60°C for 45 s, and extension at 72°C for 40 s; followed by a final extension at 72°C for 5 min.

The PCR products were verified by electrophoresis on a 3% agarose gel at 120V for 45 min. For *WNT4*, the solution for each patient consisting of 2 µL buffer, 2 µL restriction enzyme (*Hpy188III*), 10 µL PCR product, and 18 µL distilled water were gently mixed in a 1.5 mL microtube. The solutions were then incubated at 37°C for 24 h. The digested solution by the enzymes were then analyzed by gel electrophoresis on 3%GelRedstained agarose gel. We used Horizontal Electrophoresis Cell with TBE Buffer (pH = 8.3), ladder were used 50bp DNA Ladder (Thermo) after electrophoresis, the amplified PCR products were perceived under UV light. For *BMP15*, the amplified products were then digested with the restriction enzyme *MspI* (Fermentas, Germany), selected with NEBcutter software. The RFLP reaction contained 10 µL of PCR product, 2 U of *MspI*, 2 µL of buffer, and water to a final volume of 32 µL. the samples were incubated at 37°C for 16 h. The restriction patterns were examined by electrophoresis on a 3% agarose gel.

Ethics statement

The research was conducted in accordance with the WMA Declaration of Helsinki (as revised in October 2024). The study protocol was approved by the ethics committee of the Tehran Women Hospital, Iran. Informed consent was obtained from all participants prior to their inclusion in the study.

Statistical analysis

Data were analyzed with SPSS software version 18 (SPSS Inc., Chicago, IL, USA). Genotype and allele frequencies were calculated in the patient and control groups. The allele and genotype frequencies between groups was compared by the χ^2 test. The association between the studied polymorphisms and endometriosis was evaluated by calculating odds ratio (OR) and 95% confidence intervals (CI) between the study and control groups. A p -value < 0.05 was considered statistically significant.

Results

General characteristics

In this work, we measure two key characteristics of the participants including the age and body mass index (BMI), as detailed in Table 1. The participants were young adult women of 20 to 35 years old. The mean age of both groups was approximately the same 29 years old. The individuals were chosen from nearly similar body mass index, $\sim 26 \text{ kg m}^{-2}$. There is no significant difference between the mean age of two case and control groups, p value = 0.279. Similarly, we found no significant difference between the BMI of two groups, p value = 0.167 (Table 1).

Table 1 General characteristics of two case and control groups			
Characteristic	Case	Control	p -value
Age (year)	28.76 $\pm$ 6.18	29.83 $\pm$ 7.88	0.279
BMI (Kg m ⁻²)	25.63 $\pm$ 6.24	26.68 $\pm$ 4.72	0.167
The BMI stands for body mass index			
BMP15 Genotyping			

The electrophoretic pattern of the PCR products of the *BMP15* gene on the 3% agarose gel shows three distinct genotypes (Fig. 1a). The genotypes are C/C (homozygous major allele) – a single 342-bp fragment; C/T (heterozygous) – three fragments of 342, 187 and 160 bp; T/T (homozygous minor allele) – two fragments of 160 and 187 bp.

Genotype and allele frequencies of the *rs104894766* polymorphism were presented in Table 2. Accordingly, the association between the genotypes of this polymorphism and the risk of endometriosis can be determined. The CT genotype showed no significant association with endometriosis ($p = 0.2$, OR = 0.72, 95% CI 0.39–1.32). Comparison of the allele frequencies between the control and patient groups

likewise indicated that the T allele was only slightly associated with the risk of endometriosis ($p = 0.06$, OR = 0.66, 95% CI 0.42–1.03).

Table 2
Genotype and allele frequency distribution of the *BMP15* rs104894766 polymorphism in patient and control groups

Genotype	Case n (%)	Control n (%)	OR (% 95 CI)	p value
CC	51	61	1 (Reference)	-
CT	35	30	0.72 (0.39–1.32)	0.2
TT	14	8	0.48 (0.19–1.23)	0.12
Allele				
C	137	152	1 (Reference)	-
T	63	46	0.66 (0.2–1.03)	0.06

The CI and OR stand for confidence interval and the odds ratio, respectively

WNT4 Genotyping

Regarding the PCR products of the *WNT4* genes on a 3% agarose gel (Fig. 1b), there exist one fragment of 368 base pairs for G/G dominant homozygous, three fragments of 368, 208, and 160 base pairs for G/A heterozygous, and two fragments of 208 and 160 base pairs for A/A recessive homozygous. In lane 2, three bands of 368, 208, and 160 base pairs were observed which means the genotype of this individual for *WNT4* (rs121908652) is G/A heterozygous. In lane 3, only one band of 368 base pairs was observed which means the genotype of this individual for *WNT4* (rs121908652) is G/G dominant homozygous. In lane 4, two bands of 160 and 208 base pairs were observed which means the genotype of this individual for *WNT4* (rs121908652) is A/A recessive homozygous.

The genotypes of patients and controls for the *WNT4* rs121908652 polymorphism consisted of 48 cases of G/G homozygous dominant, 43 cases of G/A heterozygous, and 9 cases of A/A homozygous recessive (Table 3); while the genotype of the control group for the *WNT4* gene polymorphism includes 65 cases of G/G homozygous dominant, 29 cases of G/A heterozygous, and 6 cases of A/A homozygous recessive. The statistical analysis of the results indicates a significant relationship between the *WNT4* rs121908652 polymorphism and endometriosis at a $p < 0.05$ (Table 3).

Table 3
Genotype and allele frequency distribution of the *WNT4*
rs121908652 polymorphisms in control and patient groups

Genotype	Case	Control	OR (% 95 CI)	P value
<i>WNT4</i>	n (%)	n (%)		
GG	48	65	1 (Reference)	-
GA	43	29	0.5 (0.27–0.91)	0.02*
AA	9	6	0.49 (0.16–1.48)	0.19
Allele				
G	139	159	1 (Reference)	-
A	61	41	0.59 (0.37–0.93)	0.02*

The CI and OR stand for confidence interval and the odds ratio, respectively; the *p* values with asterisk (*) shows the statistical significant differences.

Discussion

Endometriosis and infertility are both multifactorial and polygenic diseases. Several genetic variants have been examined in relation to endometriosis, and their polymorphisms have been studied in different populations worldwide. Given the genetic background of the Iranian population and the population-specific nature of many polymorphisms, investigation of endometriosis-related polymorphisms in Iranian population is important for future research worldwide. There were significant research and advancements in the diagnosis and treatment of infertility and endometriosis, with approximately 65% of infertile couples achieving parenthood using new methods and available technologies². Genetic variants also play a pivotal role in female fertility, influencing cellular and physiological processes essential for fertility, particularly within the *WNT-BMP* gene family²¹. Different reports suggest this gene family is truly involved in development of several developmental processes such as anterior-posterior axis and oocytes development in the female reproductive and therefore fertility²⁵.

For example, members of the *BMP* family, particularly *BMP15*, acts a growth factor for oocyte derivatives by regulating proliferation and granulosa cell differentiation²¹. It was reported that mutations in *BMP*-family genes cause infertility in females²¹. The heterozygote mutation in the *BMP15* gene was diagnosed as infertile women due to ovarian hypergonadotropic failure²⁶. The *Bmp15* polymorphism has a profound impact on oocyte maturation in females²⁷. Also, the *Bmp15* mRNA expression levels were associated with endometriosis in patients²⁶.

In the present study, no significant association was observed between endometriosis and the *Bmp15* *rs104894766* polymorphism in Iranian women. Consistently, the previous studies only reported

association between *BMP15* gene polymorphism and diminished ovarian reserve²⁸ and reduced ovarian response²⁹, without any direct relationship with endometriosis in patients.

In the present work, there was a significant association between the *WNT4* (rs121908652) polymorphism and endometriosis in Iranian women. The mentioned polymorphism frequencies had an extensive increase in patients and controls. Both groups were of nearly the same age groups and body mass indexes. These characteristics were found to influence endometriosis so that the lower BMI was discussed to be related to the risk factor³⁰. Accordingly, we conducted the study within the young adult groups of nearly the same body weight to address any concerns regarding the impact of these traits on the results of the present investigation. In the present study, the GG genotype frequency of *WNT4* (rs121908652) was 48% and 65%, the GA genotype was 43% and 29% and the AA genotype was 9% and 6%, with *p* value of 0.02, suggesting that this polymorphism is related with endometriosis.

In Brazilian population, the association between four single nucleotide polymorphisms (SNPs) in *WNT4* gene family was studied, and only the *rs16826658* and *rs3820282* polymorphisms were associated with endometriosis⁶. In Chinese Han women, there was an association between *Wnt4* (rs2235529) polymorphism and endometriosis risk, while no significant association was found between endometriosis risk and three other SNPs (*rs7521902*, *rs16826658*, and *rs7515106*)³¹. In a Greek population, the SNP *rs7521902* in the *WNT4* gene was found significantly associated with endometriosis patients at genotypic level³². Accordingly, not all polymorphisms can be related to endometriosis. The genetic background of each specific population is unique and different from other populations. Additionally, it is also well known that the ultimate role of a gene or genetic variant in a particular disease is determined by its interaction with environmental factors and other genes. Thus, it is expected to observe different results due to environmental factors that has roots in societal and cultural differences as well as the level of societal advancement and the predominant lifestyle within a population²³. The present findings in Iranian population can be insightful for our understanding of etiology of endometriosis and early diagnosis.

Conclusion

This study found a correlation between the clinical and genetic findings with endometriosis risk in adult Iranian women. The *WNT4* rs121908652 polymorphism is associated with endometriosis. There was no significant relationship between the *BMP15* rs104894766 polymorphism and endometriosis in Iranian women at the genotypic level. The *WNT4* rs121908652 polymorphism may be a genetic risk factor for endometriosis in adult women.

Declarations

Authors Contribution

SRA and SMK contributed to the conceptualization, methodology, data validation, formal analysis, and visualization. SRA conducted investigation, data curation, and writing original draft. SMK prepared resources, review and editing, supervision, and project administration. Both authors have read the final manuscript and agreed to be submitted for publication.

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Declaration Statement

The authors declare no conflict of interest.

Informed Consent Statement

All the participants were informed about the tests and also further publication of the results. Then the informed consent was obtained from all the subjects engaged with the study.

Data Availability

The data generated or analyzed during this study are included in this article, the supplementary information, and the dbSNP repository with the following web links:

<https://www.ncbi.nlm.nih.gov/snp/?term=rs121908652>

<https://www.ncbi.nlm.nih.gov/snp/?term=rs104894766>

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Figures

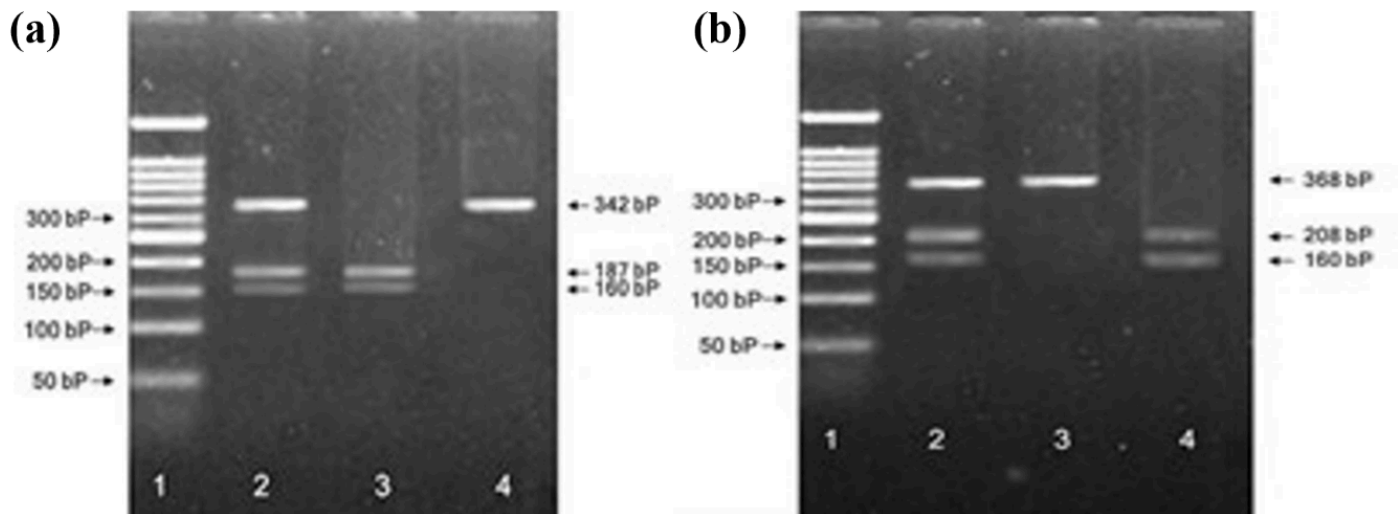


Figure 1

Results of RFLP analysis of two gene polymorphisms. (a) the *BMP15* (*rs104894766*) polymorphism; Lane 1: 50-bp molecular-weight marker; Lane 2: C/T heterozygote; Lane 3: T/T homozygous minor allele; Lane 4: C/C homozygous major allele. (b) the *WNT4* (*rs121908652*) polymorphism; Lane 1: 50-bp molecular-weight marker; Lane 2: G/A heterozygous allele; Lane 3: G/G dominant homozygous allele; Lane 4: A/A recessive homozygous allele

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