Submitted: 01 June, 2025 Accepted: 18 September, 2025 Online Published: 12 December, 2025 DOI:10.22514/j.androl.2025.040

ORIGINAL RESEARCH

REV INT ANDROL
Revista Internacional de Andrología

MMP and IL-8 gene variations in patients diagnosed with benign prostatic hyperplasia

Hakan Akdere[1,*], Nevra Alkanli[2,†], Arzu Ay[3,†], Gokhan Cevik[1], Muhidin Hassan Ibrahim[1]

[1]Department of Urology, Faculty of Medicine, Trakya University, 22030 Edirne, Türkiye
[2]Department of Biophysics, Faculty of Medicine, Haliç University, 34060 Istanbul, Türkiye
[3]Department of Biophysics, Faculty of Medicine, Trakya University, 22030 Edirne, Türkiye

***Correspondence**
hakanakdere@trakya.edu.tr
(Hakan Akdere)

† These authors contributed equally.

Abstract

Background: The study aimed to determine the frequency and prognostic relevance of Matrix Metalloproteinase (MMP) and Interleukin 8 (IL-8) gene variations in patients diagnosed with benign prostatic hyperplasia (BPH). **Methods**: The genotypes were analyzed by restriction fragment length polymorphism (RFLP) and polymerase chain reaction (PCR), and their proportions in the patient and control groups were evaluated. **Results**: The TT genotype of MMP-2(-735 C/T) was more common in the patient group compared with the control group ($p = 0.010$). In addition, the frequency of the 5A/5A genotype of MMP-3(-1171 5A/6A) was significantly higher among the patients ($p = 0.033$). The proportion of individuals with the TT genotype of IL-8(-251 A/T) was also much higher in the patient group compared with the control group ($p < 0.001$). On one hand, compared with the controls, the patients had significantly higher frequencies of the 1G/2G-6A/6A and 2G/2G-5A/6A haplotypes of MMP-1/MMP-3 ($p = 0.007$ and $p = 0.036$, respectively), the TT-CC haplotype of IL-8/MMP-2 ($p = 0.015$), and the TT-6A/6A haplotype of IL-8/MMP-3 ($p = 0.028$). On the other hand, certain genotypes and haplotypes were identified as protective factors against BPH. **Conclusions**: We identified potential genetic biomarkers of BPH that may provide novel insights into disease development, progression, and prevention, and aid in the development of novel therapeutic approaches and personalized treatments.

Keywords

Benign prostatic hyperplasia; Inflammation; Genetic variations; PCR; RFLP

Variaciones de los genes MMP e IL-8 en pacientes con diagnóstico de hiperplasia prostática benigna

Resumen

Antecedentes: Determinar la frecuencia y relevancia pronóstica de las variaciones génicas de Matrix Metalloproteinase (MMP) e Interleukin 8 (IL-8) en pacientes diagnosticados con hiperplasia prostática benigna (HPB). **Métodos**: Los genotipos se analizaron mediante polimorfismos de longitud de fragmentos de restricción (RFLP) y reacción en cadena de la polimerasa (PCR), y se evaluaron sus proporciones en los grupos de pacientes y control. **Resultados**: El genotipo TT de MMP-2(-735 C/T) fue más común en el grupo de pacientes en comparación con el grupo control ($p = 0.010$). Además, la frecuencia del genotipo 5A/5A de MMP-3(-1171 5A/6A) fue significativamente mayor entre los pacientes ($p = 0.033$). La proporción de individuos con el genotipo TT de IL-8(-251 A/T) también fue mucho mayor en el grupo de pacientes en comparación con el grupo control ($p < 0.001$). Además, en comparación con los controles, los pacientes tuvieron frecuencias significativamente más altas de los haplotipos 1G/2G-6A/6A y 2G/2G-5A/6A de MMP-1/MMP-3 ($p = 0.007$ y $p = 0.036$ respectivamente), el haplotipo TT-CC de IL-8/MMP-2 ($p = 0.015$) y el haplotipo TT-6A/6A de IL-8/MMP-3 ($p = 0.028$). Por otro lado, ciertos genotipos y haplotipos fueron identificados como factores protectores contra la HBP. **Conclusiones**: Identificamos posibles biomarcadores genéticos de la HBP que pueden proporcionar nuevos conocimientos sobre el desarrollo, progresión y prevención de la enfermedad, y ayudar en el desarrollo de nuevos enfoques terapéuticos y tratamientos personalizados.

Palabras Clave

Hiperplasia prostática benigna; Inflamación; Variaciones genéticas; PCR; RFLP

1. Introduction

Benign prostatic hyperplasia (BPH) is a common condition of the lower urinary tract that usually afflicts older men. BPH is one of the most common reasons why people experience difficulties in their lower urinary tract. The prevalence of BPH increases with age, with approximately 70–80% of the affected individuals being over the age of 80 years. It is characterized by the obstruction of the bladder outlet, which may cause structural changes in the bladder muscle, urinary distension, and bladder stones [1]. Furthermore, BPH has also been linked to various complications, such as acute urinary retention, urinary tract infections, urinary tract stones, and acute renal failure [2]. The symptoms of BPH include increased urgency to urinate and hesitation [3], which have an adverse impact on general health and quality of life. The mechanistic basis of BPH is steroid-induced cellular proliferation, which causes prostate hypertrophy and an inflammatory reaction to local infections. Histologically, BPH is defined by the development of connective tissue, smooth muscle, and glandular epithelial tissue in the prostate transition zone [4–6].

Although little is known regarding the genetic predisposition to BPH, differences in genes linked to growth factors, apoptosis, inflammation, and enzymes have been implicated in its pathophysiology. In fact, several studies have reported a strong link between genetic variations and prostate enlargement. Nevertheless, there are currently no established genetic biomarkers for the early diagnosis of BPH, thus warranting the molecular profiling of BPH patients to identify novel diagnostic markers and therapeutic targets. Given the key role of chronic prostate inflammation in the development of BPH, variations in cytokine genes involved in the inflammatory response may impact disease development and course by affecting cytokine expression levels. In addition, cytokine gene variations linked to BPH can help predict disease risk and offer new insights into the pathophysiological mechanisms [7–9]. Cytokines are bioactive molecules that regulate various biological processes, like cell proliferation, inflammation, and immune responses, through autocrine, paracrine, and endocrine mechanisms [10, 11]. Interleukin-8 (IL-8) is a critical factor in the development of prostate tissue, and is often elevated in prostate epithelial cells. However, high levels of IL-8 can induce the expression of fibroblast growth factor (FGF)-2 in the prostate, resulting in abnormal proliferation, tissue remodeling, and damage [2, 12]. In addition, matrix metalloproteinases (MMPs), which degrade cell membrane components and the extracellular matrix, also play a role in inflammation through the production and secretion of cytokines, cell growth factors, and adhesion molecules [13].

In this study, we assessed the distribution of IL-8 and MMP gene variants among BPH patients and healthy controls to identify potential biomarkers for the early diagnosis and risk assessment of BPH.

2. Materials and methods

2.1 Selection of BPH patients and healthy controls

Protocol code TÜTF-GOBAEK 2023/145 was obtained from the Trakya University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. In addition, informed consent forms were voluntarily signed by all participants prior to the study. Our study was carried out between 27 March 2023 and 27 March 2025. Ninety-one healthy controls and 91 patients with BPH were selected for this study based on specific criteria. Participants who were diagnosed with blood coagulation disorders or any form of cancer were excluded. The inclusion criteria for BPH patients were as follows: (1) prostate volumes over 40 cc, (2) complaints about urination, and (3) Qmax rate below 15 mL/s in the uroflowmetry test. The symptoms of the patients were evaluated using the International Prostate Symptom Score (IPSS) questionnaire, and the uroflowmetry test was performed at the urology outpatient clinic. Prostate volumes were measured using transabdominal ultrasonography (USG), and the Prostate Specific Antigen (PSA) values of the patients were measured. Multiparametric prostate Magnetic Resonance Imaging (MRI) was performed for patients with a PSA value $\geq$3, and biopsy was performed for patients with Prostate Imaging–Reporting and Data System (PIRADS) score $\geq$3. Treatment options included alpha-blockers and/or dutasteride, and Transurethral Prostatectomy (TURP) was performed on patients unresponsive to pharmacological treatment. Patients with a malignant biopsy result in the pathology report were excluded from the study.

2.2 Genotypic analysis

Peripheral blood samples were obtained from healthy individuals and BPH patients during routine examinations. The samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA). DNA was extracted using the Total DNA Blood Isolation Kit according to the manufacturer's protocol. Briefly, 200 μL blood was mixed with 20 μL proteinase K and 20 μL RNAse A, vortexed, and left undisturbed for 2 minutes. After adding 200μL PureLink Genomic Lysis and Binding Buffer, the samples were vortexed, incubated at 55 °C for 10 minutes, and mixed with 200 μL ethanol and vortexed for 5 seconds. The samples were dispensed into columns and centrifuged at 10,000 g for 1 minute with 500 μL Wash Buffer 1, and then with 500 μL Wash Buffer 2 at 10,000 g for 3 minutes. The columns were then placed into sterile Eppendorf tubes, and 200 μL Elution Buffer was added. After incubating at room temperature for 1 minute, the tubes were centrifuged at 10,000 g for 1 minute to elute the DNA [14]. The DNA samples were quantified using the NanoDrop spectrophotometer (UV-Vis spectrophotometer, Thermo Scientific™, Madison, WI, USA), and the purity of the samples was determined by measuring the absorbance at 260 nm and 280 nm; a 260/280 ratio ranging from 1.8–2 confirmed the absence of proteins, phenol, and other components. In addition, the quality of the DNA samples was determined by 0.8% agarose gel electrophoresis. The DNA samples that did not meet the required purity and quality standards were discarded, and the extraction procedure was repeated. The MMP and IL-8 gene sequences were amplified by PCR [15], and the genetic

variants were detected using the restriction fragment length polymorphism (RFLP) method [16]. The DNA fragments were separated by agarose gel electrophoresis. The MMP-1(-1607 1G/2G), MMP-2(-735 C/T), MMP-3(-1171 5A/6A), and IL-8(-251 A/T) gene sequences were digested using PdmI (XmnI), HinfI, PsyI (Tth111I), and VspI (AseI) respectively, which yielded fragments of 113 bp, 391 bp, 129 bp, and 173 bp. The following genotypes were detected for the different gene variants: MMP-1(-1607 1G/2G)-1G/1G (102 bp, 11 bp), 1G/2G (113 bp, 102 bp, 11 bp), and 2G/2G (113bp); MMP-2(-735 C/T)-TT (338 bp, 53 bp), CT (391 bp, 338 bp, 53 bp), and CC (391 bp); MMP-3(-1171 5A/6A)-5A/5A (96bp), 5A/6A (129 bp, 96 bp), and 6A/6A (129 bp); IL-8(-251 A/T)-AA (152 bp, 21 bp), AT (173 bp, 152 bp, 21 bp), and TT (173 bp). The primer sequences, PCR conditions, and restriction enzymes used in RFLP have been listed in **Supplementary Table 1**. Details regarding the PCR products and reagents utilized for PCR and RFLP can be found in **Supplementary Table 2**.

2.3 Statistical analysis

The statistical analysis of the study data was performed using IBM SPSS (Statistics Package for the Social Sciences, IBM Corp., 20.0, Armonk, NY, USA) Statistics for Windows. The threshold for statistical significance was set as $p < 0.05$. The demographic and clinical data of the patients and control groups were compared and evaluated using logistic regression analysis and independent samples test respectively. The distribution of the different genotypes and haplotypes was determined using the chi-squared test and logistic regression. Hardy-Weinberg equilibrium test was used to evaluate the conformity of allele frequencies.

3. Results

The demographic and clinical characteristics of the BPH patients and healthy individuals have been summarized in **Supplementary Table 3**. The average age of the patients and healthy controls were comparable (66.396 ± 7.492 years *vs.* 64.714 ± 7.618 years) with no statistically significant difference ($p = 0.263$). On the other hand, the incidence of hypertension ($p < 0.001$), diabetes mellitus ($p < 0.001$), cholesterol ($p = 0.005$), family cancer history ($p = 0.033$), heart disease ($p = 0.008$), and smoking ($p = 0.009$) were significantly different between the two groups. The trend of alcohol consumption was also similar in the patient and control groups ($p = 0.074$).

We did not detect any notable difference in the distribution of MMP-1(-1607 1G/2G) genotypes between the patient and control groups ($p > 0.05$). The frequency of the TT genotype of MMP-2(-735 C/T) was significantly higher among the BPH patients ($p = 0.010$), while the CT genotype was more frequent in the control group ($p = 0.003$). The frequency of the 5A/5A genotype of MMP-3(-1171 5A/6A) was also significantly higher among the patients ($p = 0.033$). The TT genotype of IL-8(-251 A/T) was notably more common in the patient group ($p < 0.001$), whereas the AT genotype was detected at a higher frequency in the control group ($p < 0.001$). The results are shown in Table 1.

According to the Hardy-Weinberg test, the distribution of MMP-1 and MMP-2 alleles differed notably between the patients and controls ($p < 0.05$). The distribution of MMP-3 alleles among the patients deviated significantly from the expected Hardy-Weinberg equilibrium ($p < 0.05$). In the control group, the distribution of IL-8 alleles was significantly different ($p < 0.001$). The results are shown in **Supplementary Table 4**.

We also analyzed the distribution of haplotypes in the patient and control groups. The frequency of the 2G/2G-CT haplotype of MMP-1/MMP-2 was notably higher in the control group ($p = 0.025$). Furthermore, the 1G/2G-6A/6A and 2G/2G-5A/6A haplotypes of MMP-1/MMP-3 were more common among the patients ($p = 0.007$; $p = 0.036$), while 2G/2G-6A/6A haplotype was more common among the controls ($p < 0.001$). The CT-6A/6A haplotype of MMP-2/MMP-3 was detected more frequently in the control group ($p = 0.006$). The AT-1G/1G haplotype of IL-8/MMP-1 was notably more common among the controls ($p = 0.040$). For IL-8/MMP-2 variants, the TT-CC haplotype was more common in the patient group ($p = 0.015$), while the AT-CC and AT-CT haplotypes were more prevalent in the control group ($p = 0.033$; $p = 0.017$). Furthermore, the frequency of the TT-6A/6A haplotype of IL-8/MMP-3 was higher in the patient group ($p = 0.028$), whereas the AT-6A/6A haplotype was more common in the control group ($p < 0.001$). The results are shown in Table 2.

The distribution of MMP-1(-1607 1G/2G), MMP-2(-735 C/T), MMP-3(-1171 5A/6A), and IL-8(-251 A/T) genotypes were also compared according to comorbidities. The 2G/2G genotype of MMP-1(-1607 1G/2G), TT genotype of MMP-2(-735 C/T), 5A/5A genotype of MMP-3(-1171 5A/6A), and the TT genotype of IL-8(-251 A/T) were detected at significantly higher frequencies ($p < 0.05$; **Supplementary Table 5**).

4. Discussion

BPH is a prevalent condition in aging men, and is influenced by hormonal, genetic, and immunological factors [7]. In addition, genetic variations have been linked to the development and progression of BPH [2], and genetic predisposition accounts for approximately 40–70% of the variability in BPH and excretory symptoms [17]. The clinical manifestations of BPH are associated with prostate enlargement and prostate smooth muscle tension, and enlarged prostate has been linked to hormonal changes and chronic inflammation [7]. Nevertheless, since BPH is a complex disease in terms of etiology and pathogenesis, only symptomatic treatment options are available. Additionally, due to its polygenic and multifactorial nature, it is challenging to identify the causative genes of BPH. Evaluation of genetic variations associated with BPH, either individually or in combination, may help in the screening of individuals at high risk and the implementation of preventive measures. To this end, we evaluated the genetic variations in the MMP and IL-8 genes, which are related to inflammation, in BPH patients and healthy controls. In a previous study, IL-8 levels were found to be significantly higher in prostate cancer tissues compared to BPH tissues [18]. Furthermore, MMP-1 promoter gene variants have been identified as significant factors in the development of prostate cancer [19], while variants of MMP-3 and MMP-9 genes are linked to an elevated risk of prostate cancer [20]. Likewise, MMP-1 levels

TABLE 1. Genotypic distribution of MMP-1(-1607 1G/2G), MMP-2(-735 C/T), MMP-3(-1171 5A/6A), and IL-8(-251 A/T) in BPH patients and healthy controls.

Genotype distributions	Patient group (n = 91) and Control group (n = 91)	*p*
MMP-1(-1607 1G/2G)		
1G/1G	OR: 0.905 (0.488–1.680)	0.753[a]
1G/2G	OR: 1.454 (0.764–2.768)	0.255[a]
2G/2G	OR: 0.792 (0.434–1.443)	0.445[a]
MMP-2(-735 C/T)		
CC	OR: 1.488 (0.830–2.671)	0.182[a]
CT	OR: 0.403 (0.221–0.736)	0.003[a,*]
TT	OR: 7.417 (1.623–33.892)	0.010[a,*]
MMP-3(-1171 5A/6A)		
5A/5A	OR: 2.757 (1.083–7.015)	0.033[a,*]
5A/6A	OR: 1.052 (0.562–1.969)	0.873[a]
6A/6A	OR: 0.611 (0.339–1.102)	0.102[a]
IL-8(-251 A/T)		
AA	OR: 1.280 (0.577–2.842)	0.544[a]
AT	OR: 0.317 (0.169–0.593)	<0.001[a,*]
TT	OR: 4.185 (1.905–9.195)	<0.001[a,*]

[a]*Logistic regression, Chi-square test. *Significance ($p < 0.05$).*
OR: Odds ratio; CC: Cytosine-Cytosine; CT: Cytosine-Thymine; TT: Thymine-Thymine; 1G/1G: 1Guanine/1Guanine; 1G/2G: 1Guanine/2Guanine; 2G/2G: 2Guanine/2Guanine; 5A/5A: 5Adenine/5Adenine; 5A/6A: 5Adenine/6Adenine; 6A/6A: 6Adenine/6Adenine; AA: Adenine/Adenine; AT: Adenine-Thymine; MMP: matrix metalloproteinase.

TABLE 2. Haplotype analysis, frequencies, and odds ratio values for MMP-1(-1607 1G/2G), MMP-2(-735 C/T), MMP-3(-1171 5A/6A), and IL-8(-251 A/T) in BPH patients and healthy controls.

	Patient (N = 91)	Frequency (%)	Controls (N = 91)	Frequency (%)	OR: 95% CI, *p*
Haplotype analysis MMP-1/MMP-2					
1G/1G-CC	16	17.6	13	14.3	OR: 1.280 (0.577–2.842), $p = 0.544$
1G/1G-CT	8	8.8	16	17.6	OR: 0.452 (0.183–1.116), $p = 0.085$
1G/1G-TT	5	5.5	3	3.3	OR: 1.705 (0.395–7.358), $p = 0.474$
1G/2G-CC	14	15.4	13	14.3	OR: 1.091 (0.482–2.472), $p = 0.835$
1G/2G-CT	11	12.1	10	11.0	OR: 1.114 (0.448–2.768), $p = 0.817$
2G/2G-CC	18	19.8	13	14.3	OR: 1.480 (0.677–3.232), $p = 0.326$
2G/2G-CT	11	12.1	23	25.3	OR: 0.407 (0.185–0.894), $p = 0.025$*
Haplotype analysis MMP-1/MMP-3					
1G/1G–5A/5A	8	8.8	3	3.3	OR: 2.827 (0.725–11.020), $p = 0.134$
1G/1G–5A/6A	9	9.9	17	18.7	OR: 0.478 (0.201–1.137), $p = 0.095$
1G/1G–6A/6A	11	12.1	8	8.8	OR: 1.427 (0.546–3.730), $p = 0.469$
1G/2G–5A/5A	2	2.2	5	5.5	OR: 0.387 (0.073–2.046), $p = 0.264$
1G/2G–5A/6A	7	7.7	8	8.8	OR: 0.865 (0.300–2.493), $p = 0.788$
1G/2G–6A/6A	22	24.2	8	8.8	OR: 3.308 (1.386–7.895), $p = 0.007$*
2G/2G–5A/5A	6	6.6	3	3.3	OR: 2.071 (0.502–8.546), $p = 0.314$
2G/2G–5A/6A	14	15.4	5	5.5	OR: 3.127 (1.077–9.085), $p = 0.036$*
2G/2G–6A/6A	12	13.2	34	37.4	OR: 0.255 (0.121–0.534), $p < 0.001$*

TABLE 2. Continued.

	Patient (N = 91)	Frequency (%)	Controls (N = 91)	Frequency (%)	OR: 95% CI, *p*
Haplotype analysis MMP-2/MMP-3					
CC-5A/5A	5	5.5	3	3.3	OR: 1.705 (0.395–7.358), $p = 0.474$
CC-5A/6A	18	19.8	10	11.0	OR: 1.997 (0.866–4.604), $p = 0.105$
CC-6A/6A	25	27.5	26	28.6	OR: 0.947 (0.496–1.809), $p = 0.869$
CT-5A/5A	10	11.0	5	5.5	OR: 2.124 (0.696–6.480), $p = 0.186$
CT-5A/6A	7	7.7	15	16.5	OR: 0.422 (0.163–1.091), $p = 0.075$
CT-6A/6A	13	14.3	29	31.9	OR: 0.356 (0.171–0.743), $p = 0.006$*
TT-6A/6A	7	7.7	3	3.3	OR: 2.444 (0.612–9.767), $p = 0.206$
Haplotype analysis IL-8/MMP-1					
AA-1G/1G	4	4.4	3	3.3	OR: 1.349 (0.293–6.204), $p = 0.701$
AA-1G/2G	4	4.4	3	3.3	OR: 1.349 (0.293–6.204), $p = 0.701$
AA-2G/2G	8	8.8	7	7.7	OR: 1.157 (0.401–3.334), $p = 0.788$
AT-1G/1G	16	17.6	28	30.8	OR: 0.480 (0.238–0.966), $p = 0.040$*
AT-1G/2G	16	17.6	20	22.0	OR: 0.757 (0.364–1.577), $p = 0.457$
AT-2G/2G	12	13.2	20	22.0	OR: 0.539 (0.246–1.181), $p = 0.123$
TT-1G/2G	10	11.0	3	3.3	OR: 3.621 (0.963–13.625), $p = 0.057$
TT-2G/2G	12	13.2	7	7.7	OR: 1.823 (0.683–4.864), $p = 0.231$
Haplotype analysis IL-8/MMP-2					
AA-CC	12	13.2	5	5.5	OR: 2.613 (0.881–7.748), $p = 0.083$
AA-CT	2	2.2	7	7.7	OR: 0.270 (0.055–1.335), $p = 0.108$
AT-CC	19	20.9	32	35.2	OR: 0.487 (0.251–0.945), $p = 0.033$*
AT-CT	20	22.0	35	38.5	OR: 0.451 (0.235–0.865), $p = 0.017$*
AT-TT	5	5.5	2	2.2	OR: 2.558 (0.483–13.543), $p = 0.269$
TT-CC	16	17.6	5	5.5	OR: 3.669 (1.283–10.495), $p = 0.015$*
TT-CT	9	9.9	5	5.5	OR: 1.888 (0.607–5.869), $p = 0.272$
Haplotype analysis IL-8/MMP-3					
AA-5A/6A	5	5.5	5	5.5	OR: 1.000 (0.279–3.579), $p = 1.000$
AA-6A/6A	9	9.9	8	8.8	OR: 1.139 (0.419–3.096), $p = 0.799$
AT-5A/5A	9	9.9	8	8.8	OR: 1.139 (0.419–3.096), $p = 0.799$
AT-5A/6A	15	16.5	18	19.8	OR: 0.800 (0.376–1.706), $p = 0.564$
AT-6A/6A	20	22.0	42	46.2	OR: 0.329 (0.172–0.626), $p < 0.001$*
TT-5A/6A	9	9.9	4	4.4	OR: 2.387 (0.708–8.052), $p = 0.161$
TT-6A/6A	16	17.6	6	6.6	OR: 3.022 (1.125–8.120), $p = 0.028$*

OR: Odds ratio; CI: Confidence interval; CC: Cytosine-Cytosine; CT: Cytosine-Thymine; TT: Thymine-Thymine; 1G/1G: 1Guanine/1Guanine; 1G/2G: 1Guanine/2Guanine; 2G/2G: 2Guanine/2Guanine; 5A/5A: 5Adenine/5Adenine; 5A/6A: 5Adenine/6Adenine; 6A/6A: 6Adenine/6Adenine; AA: Adenine/Adenine; AT: Adenine-Thymine.

**Significance ($p < 0.05$).*

are significantly higher in prostate cancer patients compared with those with BPH, and its overexpression is associated with increased movement and invasion of prostate cancer cells [13].

In our study, the TT genotype of MMP-2(-735 C/T), 5A/5A genotype of MMP-3(-1171 5A/6A), and TT genotype of IL-8(-251 A/T) were more prevalent among the BPH patients compared with the healthy controls, whereas the CT genotype of MMP-2(-735 C/T) and AT genotype of IL-8(-251 A/T) were more prevalent in the control group. On one hand, therefore, the distribution MMP-1 and MMP-2 gene variant alleles were significantly different between the patient and control groups, while allelic distribution of MMP-3 showed differences only in the patient group. On the other hand, the distribution of IL-8 variant alleles exhibited significant differences among the controls. It is thought that this situation may be due to the uniqueness of the Thracian population with different allele distributions. Additionally, the 1G/2G-6A/6A and 2G/2G-5A/6A haplotypes of MMP-1/MMP-3, the TT-CC haplotype of IL-8/MMP-2, and the TT-6A/6A haplotype of IL-8/MMP-3 were significantly more prevalent in the BPH group. Conversely, the 2G/2G-CT haplotype of MMP-1/MMP-2, 2G/2G-6A/6A haplotype of MMP-1/MMP-3, CT-6A/6A haplotype of MMP-2/MMP-3, AT-1G/1G haplotype of IL-8/MMP-1, the AT-CC and AT-CT haplotypes of IL-8/MMP-2, and the AT-6A/6A haplotype of IL-8/MMP-3 were notably more common in the control group. In addition, the distribution of MMP and IL-8 genotypes were also compared according to comorbidities. The 2G/2G genotype of MMP-1(-1607 1G/2G), TT genotype of MMP-2(- 735 C/T), 5A/5A genotype of MMP-3(-1171 5A/6A), and the TT genotype of IL-8(-251 A/T) were detected at significantly higher frequencies.

There are some limitations in our study that ought to be considered. First, our study was restricted to a single-center with a relatively small sample size, which limits the generalizability of the findings to larger populations. The frequency of these gene variants and their impact on the development of BPH may vary among populations with different ethnic backgrounds or geographical origins. Therefore, multi-center studies with larger sample sizes are needed to confirm our results. Secondly, our study excluded environmental variables and genetic variants that may contribute to the development of BPH. Exclusion of these factors cannot fully reflect the multifactorial nature of BPH pathophysiology. Finally, we did not evaluate the frequency of the gene variants among BPH patient subgroups stratified by clinical parameters, such as urinary tract symptoms, prostate volume, and serum PSA levels. Further studies are needed to elucidate the correlation between the gene variants and these factors in more heterogeneous and larger populations to determine their clinical relevance.

The genetic biomarkers identified in this study will have to be validated in different populations and racial/ethnic groups prior to any clinical translation. Nevertheless, our findings are relevant for the early diagnosis and risk assessment of BPH. Screening for genetic risk factors in individuals with a family history of BPH, or those who exhibit symptoms at an early age, will enable identification of high-risk individuals and monitoring of more aggressive forms of the disease. Furthermore, these genetic biomarkers can supplement clinical indices to predict the risk or severity of BPH, as well as disease progression and response to treatment. Integration of genetic biomarkers is also critical for the development of personalized therapies, and can be used to predict the treatment response of patients with specific genetic profiles and select the most effective drugs. In addition, since these genetic variations can alter the expression and function of MMP and IL-8, drugs targeting the specific pathways can be developed for patients harboring these variants. In conclusion, biomarkers related to IL-8 and MMP gene variations will facilitate the development of personalized approaches to the diagnosis, prognosis, and treatment of BPH, and contribute to a more comprehensive understanding of the disease.

5. Conclusions

MMP-2(-735 T/T), MMP-3(-1171 5A/5A), and IL-8(-251 T/T) were identified as the risk factors contributing to BPH development, whereas IL-8(-251 A/T) and MMP-2(-735 C/T) were identified as protective factors that may prevent the onset of BPH. Additionally, the 1G/2G-6A/6A and 2G/2G-5A/6A haplotypes of MMP-1/MMP-3, the TT-CC haplotype of IL-8/MMP-2, and the TT-6A/6A haplotype of IL-8/MMP-3 are potential risk factors of BPH, whereas 2G/2G-CT haplotype of MMP-1/MMP-2, 2G/2G-6A/6A haplotype of MMP-1/MMP-3, CT-6A/6A haplotype of MMP-2/MMP-3, AT-1G/1G haplotype of IL-8/MMP-1, AT-CC and AT-CT haplotypes of IL-8/MMP-2, and the AT-6A/6A haplotype of IL-8/MMP-3 may be protective factors. These genetic biomarkers can not only improve our understanding of the pathological mechanisms of BPH, but can also be used for risk assessment, early diagnosis and prevention, and the development of personalized therapeutic strategies. However, the clinical relevance of these biomarkers will have to be validated in large and ethnically diverse cohorts. Nevertheless, our findings offer new insights into the molecular basis of BPH.

AVAILABILITY OF DATA AND MATERIALS

Our study data contain personal information of patients and, therefore, are not available for sharing due to the “Personal Data Protection Law” and ethical reasons.

AUTHOR CONTRIBUTIONS

HA, NA, AA—Conceptualization, formal analysis, investigation, resources, visualization, supervision; HA, NA, AA, GC—methodology, software, validation, project administration, funding acquisition; HA, AA, GC, MHI—data curation; NA, AA—writing—original draft preparation, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee approval for this study was obtained from The Ethics Committee of the Faculty of Medicine of our University, with the decision number and protocol code TÜTF-

GOBAEK 2023/145, and all procedures in this study were performed under the Declaration of Helsinki and its subsequent amendments. In addition, informed consent forms were voluntarily signed by all participants prior to the study.

ACKNOWLEDGMENT

We would like to thank this work was supported by the Department of Urology at Trakya University and the Department of Biophysics at Haliç University.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1999307556864835584/attachment/Supplementary%20material.docx

REFERENCES

[1] Ozdes AA, Canturk R, Pirincci N. Urethral stones and benign prostatic hyperplasia: presentation of a rare case. Annals of Medical Research. 2025; 32: 131–134.

[2] Daryanto B, Budaya TN, Widodo, Agustriawan D, Negara EP, Effendi RA. Analysis of gene polymorphisms in benign prostate hyperplasia patients receiving combination therapy of alpha blocker (α-Blocker) and 5-Alpha Reductase Inhibitor (5-ARI). Acta Informatica Medica. 2025; 33: 54–57.

[3] Maharani R, Lestari H, Dewa PM, Yudisthira D, Amar N, Daryanto B. A comprehensive systematic review of studies on the potential of A49T and V89L polymorphism in SRD5AR2 as high susceptibility gene association with benign prostate hyperplasia and prostate cancer. Archivio Italiano di Urologia e Andrologia. 2025; 97: 13318.

[4] Wei H, Zhu C, Huang Q, Yang J, Li YT, Zhang YG, *et al*. Global, regional, and national burden of benign prostatic hyperplasia from 1990 to 2021 and projection to 2035. BMC Urology. 2025; 25: 34.

[5] Sandhu JS, Bixler BR, Dahm P, Goueli R, Kirkby E, Stoffel JT, *et al*. Management of lower urinary tract symptoms attributed to Benign Prostatic Hyperplasia (BPH): AUA guideline amendment 2023. Journal of Urology. 2024; 211: 11–19.

[6] Lin L, Wang W, Shao Y, Li X, Zhou L. National prevalence and incidence of benign prostatic hyperplasia/lower urinary tract symptoms and validated risk factors pattern. The Aging Male. 2025; 28: 2478875.

[7] Inamura S, Terada N. Chronic inflammation in benign prostatic hyperplasia: pathophysiology and treatment options. International Journal of Urology. 2024; 31: 968–974.

[8] Yoo KH, Kim SK, Chung JH, Chang SG. Association of IL10, IL10RA, and IL10RB polymorphisms with benign prostate hyperplasia in Korean population. Journal of Korean Medical Science. 2011; 26: 659–664.

[9] Jurecekova J, Babusikova E, Kmetova Sivonova M, Drobkova H, Petras M, Kliment J, *et al*. Association between interleukin-18 variants and prostate cancer in Slovak population. Neoplasma. 2017; 64: 148–155.

[10] Wang SY, Cai Y, Hu X, Li F, Qian XH, Xia LY, *et al*. P. gingivalis in oral-prostate axis exacerbates benign prostatic hyperplasia via IL-6/IL-6R pathway. Military Medical Research. 2024; 11: 30.

[11] Ali SH, Abdulrahman MA, AL-Obaidi ORK. Immunological ınteractions and inflammatory changes in the pathways of benign prostatic hyperplasia and prostate cancer. Samarra Journal of Pure and Applied Science. 2025; 7: 162–169.

[12] Bahrun U, Atmanto YKAA, Nurulita A, Mangarengi F, Palinrungi MA, Bahar B. Correlation of serum interleukin-8 levels and prostate volume to the degree of lower urinary tract symptoms in patients with benign prostate enlargement: a cross-sectional study. African Journal of Urology. 2024; 30: 24.

[13] El-Chaer WK, Tonet-Furioso AC, Morais Junior GS, Souza VC, Avelar GG, Henriques AD, *et al*. Serum levels of matrix metalloproteinase-1 in brazilian patients with benign prostatic hyperplasia or prostate cancer. Current Gerontology and Geriatrics Research. 2020; 2020: 6012102.

[14] Life Technologies (US). PureLink genomic DNA isolation protocol. 2012. Available at: https://tools.thermofisher.com/content/sfs/manuals/purelink_genomic_man.pdf (Accessed: 08 August 2025).

[15] Mullis KB. The unusual origin of the polymerase chain reaction. Scientific American. 1990; 262: 56–61, 64–65.

[16] Botstein D, White RL, Skolnick M, Davis RW. Construction of a genetic linkage map in man using restriction fragment length polymorphisms. American Journal of Human Genetics. 1980; 32: 314–331.

[17] Hennenberg M, Hu S, Tamalunas A, Stief CG. Genetic predisposition to benign prostatic hyperplasia: where do we stand? European Urology Open Science. 2024; 70: 154–157.

[18] Taheri M, Noroozi R, Dehghan A, Roozbahani GA, Omrani MD, Ghafouri-Fard S. Interleukin (IL)-8 polymorphisms and risk of prostate disorders. Gene. 2019; 692: 22–25.

[19] Liao CH, Wu HC, Hu PS, Hsu SW, Shen TC, Hsia TC, *et al*. The association of matrix metalloproteinase-1 promoter polymorphisms with prostate cancer in Taiwanese patients. Anticancer Research. 2018; 38: 3907–3911.

[20] Zhou H, Zhu X. Association between matrix-metalloproteinase polymorphisms and prostate cancer risk: a meta-analysis and systematic review. Cancer Management and Research. 2018; 10: 5247–5259.

How to cite this article: Hakan Akdere, Nevra Alkanli, Arzu Ay, Gokhan Cevik, Muhidin Hassan Ibrahim. MMP and IL-8 gene variations in patients diagnosed with benign prostatic hyperplasia. Revista Internacional de Andrología. 2025. doi: 10.22514/j.androl.2025.040.