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ESR 2 ESTROGEN RECEPTOR POLYMORPHISM AND BENIGN PROSTATE HYPERPLASIA .

Annotation

It is now known that estrogens bind to two types of nuclear receptors - α and β (ERα and ER β). Estrogen receptors function according to the classical mechanism of ligand -dependent transcription with subsequent regulation of gene expression. The estrogen receptor α gene (ESR 1) is localized on the long arm of chromosome 6 (locus q 24-27). Disturbances in the ESR 1 receptor gene lead to disturbances in the sensitivity of receptors to hormones and even to its loss. The most studied polymorphism consists of a nucleatide substitution thymine to cytosine (T397C) Pvull in the first intron of the gene and replacement of adenine with guanine (A 351 G) Xbal in the intronic region of the gene. According to the literature, polymorphism in the intronic region of the ESR 1 gene (Pvull) is associated with the risk of developing MGD [15]. The important role of estrogens in the regulation of endometrial cell proliferation, angiogenesis and inflammation has also been confirmed.

Keywords: *ESR 1 , estrogen , prostate, inhibitor, BPH.*

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is the most common prostate disease in older men. Approximately 50% of men aged 51–60 years and ~90% of men aged 81–90 years have BPH (1,2). Clinically, BPH is associated with lower urinary tract symptoms (LUTS) (3). BPH is generally considered to be a benign enlargement of the prostate gland that contributes to a variety of urinary problems. The molecular etiology of BPH involves many complex processes, so the exact cause remains unknown. Various theories have been proposed, such as embryonic awakening, aging, androgens,

estrogens, and inflammation (4). Estrogen, a female hormone, plays an essential role in the development of female secondary sexual characteristics; however, it is also produced in men. Estrogen is involved in stimulating prostate growth and the development of prostate disease in men (5,6). Estrogen action is mediated by two estrogen receptors (ESRs), which can be divided into two subtypes: ESR1 (ERα) and ESR2 (ERβ) (5). However, ESR1 and ESR2 are not isoforms but are encoded by separate genes on different chromosomes (5). ESR1 and ESR2 are located on chromosome 6q25.1 and chromosome 14q23.2, respectively (7). Expression of ESR2 in the ventral prostate differs from that of ESR1. While ESR1 is typically found in prostate stromal cells, ESR2 is predominantly expressed in epithelial cells (8). The two ESRs have different physical characteristics. Different sites of expression and affinity may be associated with different biological functions of estrogens in the prostate gland (5). In adult prostate tissue, there is a gradient of ESR2 expression with low proximal levels and increased distal expression levels. This gradient may result in heterogeneity of differentiation and function along the length of the ducts. Although ESR2 is the predominant ESR expressed in the adult prostate, its role is not yet clearly defined. ESR2 may play a role in epithelial differentiation (8). ESR2 has also been suggested to have an antiproliferative role in the prostate and regulate androgen stimulation of prostate growth (8). Previously, several studies have examined the role of ESR2 in the prostate using knockout animal models. Studies have shown that ESR2 inhibits prostate proliferation and the development of prostatic hyperplasia during aging (5,10). The aim of this study was to investigate whether four single nucleotide polymorphisms (SNPs) (rs4986938, rs17766755, rs12435857 and rs1256049) of the ESR2 gene are associated with the development of BPH

Materials and methods

Subjects of study. The present study included 173 men who attended a clinic for LUTS between January 2021 and December 2022. Clinical symptoms in patients were assessed using International questionnaires Prostate Symptom Score (IPSS) and quality of life (QoL). Patients' prostate volumes were measured

using transrectal ultrasonography , and the level of prostate-specific antigen (PSA) in each subject's serum was determined. Peak urine flow rate (Qmax) and mean urine flow rate (Qavg) were measured using a uroflowmetry system .

Subjects were excluded from the study if they had prostate cancer, neurogenic bladder, urethral stricture, acute/chronic prostatitis, urinary tract infection, uncontrolled diabetes mellitus, previous pelvic surgery, or hypertension. Based on symptoms, subjects were assigned to either a control group (prostate volume <30 mL) or a BPH group [prostate volume 30 mL; IPSS, >8; Qmax , <15 ml/sec] group (11,12). All subjects provided written informed consent.

SNP selection and genotyping. A SNP database search was conducted to select ESR2 gene SNPs for study. SNPs with heterozygosity >0.1, minor allele frequency >10%, and associations with other diseases were selected . Ultimately, four promoter polymorphisms [rs4986938 (intron), rs17766755 (intron), rs12435857 (intron) and rs1256049 (Val328Val)] of the ESR2 gene were selected.

Genotypes were determined by direct sequencing. Polymerase chain reaction (PCR) was performed before sequencing. PCR was performed for 39 cycles at 94°C for 30 s, 58°C for 30 s, and 72°C for 1 min. Finally, PCR was performed at 72°C for 7 min to terminate the reaction. Each PCR product was identified by 1.8% agarose gel electrophoresis, and the products were sequenced using an ABI Prism ® 377 automated sequencer (Applied Biosystems , Foster City, California, USA). Sequence data were analyzed using SeqManII software , v2.3

Results

Statistical analysis. SNPStats was used to analyze genetic data . For each SNP in the control group, a Hardy– Weinberg equilibrium test was performed , and then logistic regression models (codominant 1, codominant 2, dominant, recessive, and logadditive) were applied to obtain odds ratios (ORs), 95% confidence intervals (CIs), and P-values. The linkage disequilibrium (LD) block

SNP of the ESR2 gene was analyzed using Haploview version 4.2 and the Gabriel algorithm et al (17). The significance level was set at $P<0.05$

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