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Original Research Article

Association between transient receptor potential melastatin genotypes and the prostate surface antigen levels in BPH patients

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ABSTRACT

Background: Benign Prostate Hyperplasia (BPH) is a prevalent condition among older males, characterized by an enlarged prostate gland leading to lower urinary tract symptoms and impacting quality of life. Transient receptor potential melastatin (TRPM) genes regulate various physiological processes.
Methods: We studied 194 BPH patients and 194 healthy controls, genotyping six selected TRPM gene SNPs. PSA levels were measured using the Cobas® e411 analyzer.
Results: Prostate-specific antigen (PSA) levels were significantly higher in BPH patients (135.76±578.03 ng/mL) than in controls (2.01±1.09 ng/mL). TRPM2 (rs168355) and TRPM7 (rs2362295) genotypes were significantly associated with elevated PSA levels. The TRPM2 GG genotype was associated with decrease in the likelihood of severe PSA levels (OR=0.34, 95% CI: 0.12-0.96, P=0.034), while the TRPM7 CC genotype showed increased odds for severe PSA levels (OR=1.48, 95% CI: 1.08-3.56, P=0.041).
Conclusions: Our findings suggest a potential link between TRPM gene variants and the severity of prostatic changes reflected in PSA secretions, indicating the need for further research to understand the underlying mechanisms and clinical implications.

Keywords: BPH SNP's, Genotype, PSA, TRPM

INTRODUCTION

Benign Prostate Hyperplasia (BPH), is a benign condition affecting more than half of the male population globally, three-quarters of whom are aged between 80-89 years old, majorly presenting with an enlarged prostate gland.[1] The transitional zone (TZ) that surrounds the urethra tends to be prominent in BPH due to the active and excessive proliferation of the stromal cells associated with dysfunctional apoptotic process.[2] The biological activities that include an imbalance of androgens, tissue changes associated with advanced age, and inflammation are known to influence the pathological and physiological process of BPH.[3] The excessive growth of the stromal cells in the prostate gland initiates an onset of Lower urinary tract symptoms (LUTS) which may manifest itself in one of three forms such as either irritative, obstructive, or both obstructive and irritative, Prostate-specific antigen is a serine protease enzyme produced by the columnar epithelium of prostatic tissue.[4] The pro-enzymatic intracellular form of PSA is pro-PSA.[5]

Following cellular production, pro-PSA passes through the basal and endothelial cell layers before entering the prostatic ducts, where it is converted to active PSA, finally penetrating the capillary membranes to enter the systemic circulation.[6] A small portion of this active PSA then undergoes proteolysis, becoming inactive or "free"

PSA when it enters the bloodstream and remains unbound. Active PSA that reaches the bloodstream rapidly becomes bound to circulating protease inhibitors.[7]

The TRPM sub family is one of the six parts and the largest sub family of the transient receptor potential channels and shares structural similarities with other TRP subfamilies.[8] It consists of six membrane-spanning regions, cytoplasmic C and N terminals, and a C-terminal motif.[9,10] Among the TRPM genes, TRPM8 is predominantly expressed in vascular smooth muscles, despite their diverse electrophysiological behaviors TRPM proteins can be classified into two major groups.[11] All TRPMs can form a functional cation channel either as homo or hetero-multimers, as demonstrated by patch-clamp measurements in the mammalian cell lines transferred with TRPM plasmid DNAS.[12]

These channels are widely expressed and contribute to cellular calcium signaling by allowing calcium entry into the cytosol in response to various stimuli.[8] This calcium entry can affect biological processes such as the sensing of oxidative stress, regulation of endothelial permeability, magnesium homeostasis, myogenic response, and regulation of vascular tone or affect the effects of other channels by modulating their membrane potentials.[13]

Members of the TRPM family have emerged as promising drug targets for various disorders including neurodegenerative disorders, cardiovascular diseases, type-II diabetes, inflammation, and inflammatory pain.[14,15] The objective of this study was to investigate the association between genetic variations in transient receptor potential melastatin (TRPM) genes and prostate-specific antigen (PSA) levels in patients with Benign Prostate Hyperplasia (BPH).

METHODS

Study population

This was an analytical cross-sectional study where a total of 194 cases diagnosed with BPH at the urology clinic at JOOTRH, (a tertiary hospital in western Kenya), and 194 controls (healthy adults male aged 40 years and above) were recruited into the study, all the patients recruited into the study met the criteria set by the American urological association, the control group consisted of healthy individuals from the same region as the BPH patients. Patients with other comorbidities were excluded from the study. The study was approved by the IERC in tandem with the Helsinki Declaration, both the control and patients were included in the study after giving informed consent. The study was done from April 2022 to August 2023

Genomic DNA was extracted from peripheral blood leukocytes using the salting out method. Genotyping was performed using Illumina® iScan Infinium with multiplex human genotyping microarrays. Six SNPs (TRPM2: rs168355, TRPM6: rs4745363, TRPM7: rs8042919, rs2362295, TRPM8: rs10490018, rs1016062) were analyzed. Criteria for SNP selection included moderate to high minor allele frequency, ability to capture genetic variation efficiently, and compatibility with the Illumina microarray assay. DNA extraction was done using the QIAamp blood kit, with ethanol precipitation and elution in buffer AE.

The criteria for choice of SNP's used were: 1) SNPs with moderate to high minor allele frequency (MAF), 2) SNPs with the ability to efficiently capture the genetic variation in a region, 3) the tag SNPs used for Illumina, 4) SNPs with known genotyping performance and SNPs that are compatible with the microarray assay design used by illumina.

The prostate surface antigen (PSA) was analyzed using the Cobas® e411 analyzer utilizing the sandwich principle, where 20 ul of serum a biotinylated PSA-specific antibody and a monoclonal PSA-specific antibody labeled with ruthenium complex reacted to form a sandwich complex, after addition of streptavidin-coated microparticles, the complex was bounded to the solid phase via interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. The unbound substance was removed with Procell/Procell M, the application of a voltage to the electrode induced chemiluminescent emission which was measured by a photomultiplier, the results were determined via a calibration curve which is an instrument specifically generated by a 2-point calibration and a master curve provided via the reagent barcode. The analyzer automatically calculated the PSA concentration of each sample in ng/mL.

Statistical analysis

The statistical package for social science (SPSS) version 27.0, (IBM® SPSS Inc Chicago IL USA) was used for data analysis. Categorical data were summarized as proportions. Continuous data such as age, were compared between the BPH patients and the control participants using the un-paired t-test. The genotype frequencies, electrolytes, and PSA levels were compared across the genotype carriers and were tested for an association between the two groups using the Chi-Square. Hardy-Weinberg equilibrium was calculated using the genome studio genotyping module of Illumina® Infinium assay. The haplotype distribution was determined by the DRAGEN haplotype variant caller algorithm an inbuilt software of the Illumina® Infinium assay. The statistical levels were recorded with a 95% confidence interval and a statistical significance was considered at $P<0.05$.

RESULTS

The socio-demographic and clinical characteristics of the study participants are summarized in Table 1. A total of

398 adult males were included in the study, comprising 194 BPH patients and 194 healthy control individuals without any known conditions. The mean age±SD was 65.47±12.55 years (range 38-92 years) for BPH cases and 64.52±12.19 years (range 39-91 years) for the healthy control group. Most BPH patients and the control group were in the age group of 70-79 years (n=53 for both groups). The age group with the least number of participants was 90-99 years for the cases (n=2) and 30-39 years for the control group (n=1). Regarding educational status, 59.01% (n=115) of the BPH patients had no formal education, while 53.09% (n=100) of the control group had no formal education. Additionally, 67.1% (n=130) of the patients resided in a rural area, while 55.1% (n=107) of the control participants lived in a rural area. The majority of the patients (63.9%, n=124) had experienced BPH symptoms for 6-12 months, while none of the healthy control participants had these symptoms. Furthermore, the severity of lower urinary tract symptoms (LUTS) was classified as severe in the majority of the patients (63.1%, n=123), moderate (22.7%, n=44), and mild (13.9%, n=27) respectively, with none of the control participants presenting with LUTS.

Table 1: Socio-demographic and clinical characteristics of the study participants.

Characteristics	Categories	BPH patients (n=194) (%)	Control group (n=194) (%)	P
Ages (yrs.)	30-39	3 (1.5)	1 (0.5)	0.827
	40-59	25 (12.9)	21 (10.8)	
	50-59	41 (21.1)	45 (23.2)	
	60-69	46 (23.7)	51 (26.3)	
	70-79	5.3 (27.3)	52 (26.8)	
	80-89	24 (12.4)	22 (11.3)	
	90-99	2 (1.0)	2 (1.0)	
Education	Formal	79 (40.72)	91 (46.90)	0.342
	Informal	115 (59.27)	103 (53.09)	
Occupation	Salaried	38 (14.43)	44 (22.68)	0.067
	Farmer	51 (26.29)	59 (30.41)	
	Business	56 (28.87)	63 (32.47)	
	Unemployed	49 (25.26)	28 (14.43)	
Residence	Urban	64 (32.9)	87 (44.9)	0.007*
	Rural	130 (67.1)	107(55.1)	
Duration of BPH symptoms	0-6 months	21 (10.82)	0 (0.00)	0.001*
	6-12months	124(63.9)	0 (0.00)	
	13-18months	46 (23.7)	0 (0.00)	
	>18months	03 (1.5)	0 (0.00)	
LUTS severity	Mild IPSS 0-7	27 (13.9)	0 (0.00)	0.000*
	Moderate IPSS (8-19)	44 (22.7)	0 (0.00)	
	Severe IPSS (20-35)	123 (63.4)	0 (0.00)	

*Statistically significant.

Table 2: PSA levels among the patients and control groups.

PSA levels	Normal	Mild	Moderate	Severe	Total
BPH patients	3	19	41	131	194
Control group	191	3	0	0	194
Total	194	22	41	131	388

Key: Normal (0- 4 mmol/L), Moderate (10- 20 mmol/L), Severe (> 20 mmol/L)

The mean PSA levels were significantly higher among BPH patients, with a mean of 135.76±578.03, compared to the control group, which had a mean of 2.01±1.09.

PSA biomarker measurements showed that 1.5% (n=3) of the patients had normal secretion, 9.8% (n=19) had mild secretion, 21.3% (n=41) had moderate secretion, and 67.5% (n=131) had severe secretion. In contrast, none of the control group participants had moderate or severe PSA secretion. However, 1.5% (n=3) of the control participants had mild secretion as shown in Table 2.

Among the BPH patients, PSA levels were distributed as follows: 1.6% (3) normal, 9.8% (19) mild, 21.1% (41) moderate, and 67.5% (131) severe. In the control group, PSA levels were distributed as follows: 98.5% (191) normal and 1.5% (3) mild. The study found a statistically significant difference in PSA levels between the BPH patients and the control group ($p<0.001$), with a chi-square value of 365.82 and a degree of freedom of 3.

Association between age distribution and PSA level

Out of the 388 patients in the study, PSA levels were distributed as follows: 50% (194) had normal PSA levels, 5.7% (22) were mild, 10.6% (41) were moderate, and 33.8% (131) had severe levels. A statistically significant association was found between age distribution and PSA levels ($p < 0.0001$), with a chi-square value of 267.3 and a degree of freedom of 168 (Table 3).

Association between the 6 SNP's and the PSA level among the BPH patients

The study investigated the association between six SNP's and PSA levels among BPH patients, revealing a significant association as presented in Table 4. For TRPM2 (rs168355), the GG genotype was significantly associated with reduced odds of severe PSA levels compared to the TT genotype (OR=0.34, 95% CI: 0.12-0.96, P=0.034).

Similarly, TRPM7 (rs2362295) showed an association, with the CC genotype indicating increased odds of severe PSA levels (OR=1.48, 95% CI: 1.08-3.56, P=0.041). However, the other genes studied did not exhibit any statistical significance in their association with PSA levels.

Table 3: Association between age distribution and PSA level.

	Group	N	Mean	STD	SEM
Ages	Cases	194	65.41	12.55	0.90
	Control	194	64.57	12.06	0.87
PSA	Cases	194	135.76	578.03	41.50
	Control	194	2.01	1.09	0.079

Table 4: The association between SNP's and PSA levels among BPH patients.

Gene	Genotype	PSA level (n=194)				OR (95%CI)	P
		Normal (<4ng/ml)	**Mild (4.1-10.0ng/ml)**	**Moderate (10.1-20.0ng/ml)**	**Severe >20ng/ml**		
TRPM2 rs168355	TT	00 (0.00)	01 (0.52)	04 (2.06)	33 (17.01)	2.49 (2.27-5.09)	0.034*
	TG	00 (0.00)	00 (0.00)	03 (1.55)	12 (6.19)	1.42 (1.24-3.65)	0.768
	GG	00 (0.00)	00 (0.00)	04 (2.06)	16 (8.24)	0.34 (0.12-0.96)	0.456
TRPM6 rs4745363	TT	00 (0.00)	00 (0.00)	01 (0.52)	05 (2.58)	1.88 (1.39-2.56)	0.296
	TA	00 (0.00)	00 (0.00)	00 (0.00)	03 (1.55)	1.49 (0.63-3.21)	0.345
	AA	00 (0.00)	00 (0.00)	01 (0.52)	04 (2.06)	1.34 (0.86-1.99)	0.561
TRPM7 rs8042919	GG	01 (0.52)	03 (1.55)	04 (2.06)	04 (2.06)	1.34 (0.79-1.95)	0.534
	GA	00 (0.00)	04 (2.06)	02 (1.03)	02 (1.03)	1.24 (0.64-3.43)	0.674
	AA	01 (0.52)	06 (3.09)	01 (0.52)	01 (0.52)	1.35 (0.27-6.32)	0.891
TRPM7 rs2362295	CC	00 (0.00)	00 (0.00)	08 (4.12)	22 (11.34)	1.48 (1.08-3.56)	0.041*
	CT	00 (0.00)	00 (0.00)	04 (2.06)	12 (6.19)	0.85 (0.32-1.89)	0.287
	TT	00 (0.00)	00 (0.00)	03 (1.55)	08 (4.12)	0.53 (0.15-3.25)	1.023
RPM8 rs10490018	CC	01 (0.52)	02 (1.03)	02 (1.03)	02 (1.03)	1.16 (0.64-1.43)	0.789
	CT	00 (0.00)	03 (1.55)	01 (0.52)	01 (0.52)	1.47 (0.42-4.38)	0.764
	TT	00 (0.00)	00 (0.00)	01 (0.52)	02 (1.03)	1.20 (0.04-2.71)	0.589
TRPM8 rs1016062	GG	00 (0.00)	00 (0.00)	02 (1.03)	01 (0.52)	1.35 (0.88-1.60)	0.591
	GA	00 (0.00)	00 (0.00)	00 (0.00)	03 (1.55)	1.07 (0.61-1.88)	1.004
	AA	00 (0.00)	00 (0.00)	00 (0.00)	00 (0.00)	0.83 (0.51-1.29)	0.456
Total		03 (1.54)	19 (9.79)	41 (21.13)	131 (67.53)		

*Statistically significant.

DISCUSSION

Our study found that the mean PSA levels were significantly higher among BPH patients, with a mean of 135.76±578.03, compared to the control group, which had a mean of 2.01±1.09. This is in contrast to another study in Nigeria, where the mean PSA level was 76.59.[16] A study conducted among men in Australia showed that the average PSA levels in patients with BPH were 109.02.[17] According to another study, the mean PSA levels among the BPH patients in South Africa was 21.59±3.78, a level which is quite lower compared to this study.[18] In Iraq study on the PSA antigen ratio in BPH and Pca patients revealed a mean PSA level of 124.12±21 which corroborated with this study.[19] Inflammation, a crucial symptom of BPH, is widely recognized for its significant role in the development and pathogenesis of the condition. The growth of the prostate is affected by an imbalance between the growth of prostatic cells and their natural cell death.[20] The patients with inflamed prostate glands present with higher levels of PSA due to enhanced growth and multiplication of the stromal cells which leads to higher secretion of the PSA marker.[21]

Prostate surface antigen (PSA) levels are a vital marker in evaluating the health of the prostate, this study established an association between TRMP2 (rs168355) and TRMP7 (rs2362295) genotypes and PSA levels.[22] The TRPM2 GG genotype was associated with reduced odds of severe levels of PSA while the TRPM7 CC genotype showed an increased odds ratio for severe PSA levels. This suggests a potential link between TRPM gene variants and the severity of prostatic changes reflected in PSA levels. It has been observed that overexpression of TRPM2 is induced by tissues undergoing remodeling, apoptosis, and ROS. The High oxidative stress in the prostate may activate TRPM2 interactions with other cellular pathways leading to an influx of cations, this influx could contribute to cellular response including secretion of (PSA).[23]

Several TRP channels have been shown to mediate oxidative-stress-induced injury.[24] Early studies on the function of the TRPM2 channel support the paradigm that activation of TRPM2-induced cell death by sustained increase in calcium ions or by enhanced cytokine production, which was associated with increased inflammation and tissue injury.[25-27] TRPM2 plays a key role in the proliferation of the prostate cell lines, it is potentially expressed in the plasma membrane and the cytosol such as in lysosomes, and localized in the nuclei too.[28,29] It provides this desired specificity through a variety of mechanisms. Namely, overexpression in SCC9 and SCC25 cells, and promotion of apoptotic cell death upon activation by oxidative stress. Recently, the presence of TRPM2 has been demonstrated in laser microdissected, tumoral epithelial, and human prostate cells using quantitative RT-PCR. The analysis showed a high expression of TRPM2 transcripts in 75% of the prostatic benign epithelial cells in comparison to the matched microdissected healthy cells of the surgical specimens. TRPM7 is ubiquitously exposed in the human body and has a dual function as an ion channel and serine/threonine kinases, more importantly, involved in the homeostasis of Mg^{2+}/Ca^{2+} and activated by various stimuli such as osmolarity and intracellular cations.[30] Ca^{2+} /Mg^{2+} ratio in the prostate is thought to increase the Ca^{2+} influx mediated by TRPM7 which promotes cell proliferation in BPH in addition it is assumed that TRPM7 is somehow involved in cell death induction under pathophysiological conditions through overexpression of the HEK923.[30-32]

The limitation of this study was the use of a relatively small sample size, which may have limited the generalizability of the findings. Additionally, the study focused on a specific population in western Kenya, which may limit the extrapolation of the results to other populations. Furthermore, while efforts were made to control for confounding factors, there may still be other unmeasured variables that could have influenced the results.

CONCLUSION

This study identified significant associations between genetic variations in TRPM2 and TRPM7 genes and elevated PSA levels in BPH patients. The findings suggest that TRPM CC, and TRPM2 TT genotypes may be linked to the severity of prostatic changes reflected in PSA secretions. Additional investigation is needed to clarify the pathophysiological relationship between the TRPM2 (rs168355) and TRPM7 (rs2362295) genotypes, which are linked to increased PSA levels, in order to implement precise gene therapy interventions.

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