RESEARCH ARTICLE

Editorial Process: Submission:29/07/2025 Acceptance:05/08/2026 Published:20/08/2026

Association of Single-Nucleotide Polymorphisms, rs693 and rs1042031, in the *APOB* Gene with the Risk of Prostatic Diseases among Lebanese Males

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Abstract

Purpose: Examining the relationship of the single-nucleotide polymorphisms (SNPs) rs693C>T and rs1042031G>A in the APOB gene with the risks of prostatic diseases and identifying candidate common genetic markers for prostate cancer (PCa) and benign prostate hyperplasia (BPH) in Lebanese men. **Materials and Methods:** Blood leukocyte DNA from 177 individuals (including 63 healthy subjects, 59 individuals with confirmed PCa, and 55 individuals with clinical BPH) was genotyped using the PCR-RFLP method. Associations were assessed by calculating odds ratios (ORs) based on allele frequencies and genotype distributions in the control and affected groups. A p-value <0.05 was considered significant. **Results:** The genotypic ratios for four of the eight categories for the two SNPs were in Hardy-Weinberg equilibrium. The X allele of rs693 was more common in the BPH group (p=0.03), PCa group (p=0.09), and the PCa+BPH combined affected group (p=0.03) compared to the control group. The E allele of rs1042031 was more common in the PCa group (p=0.03) but not in the BPH group (p=0.19) or the PCa+BPH combined affected group (p=0.37). Combination genotype and haplotype analyses indicated a higher prevalence of the X and E alleles and the XE haplotype in the affected groups compared to the control group ($p < 0.05$). **Conclusions:** The X allele of rs693, the E allele of rs1042031, and the XE haplotype are potentially associated with increased risk of PCA and BPH among Lebanese men. Further functional studies are necessary to validate these findings. The small sample size and the sampling from a single ethnic group are limitations of this study.

Keywords: *APOB* gene, SNP Association Study, Prostate Cancer, Benign Prostate Hyperplasia

Asian Pac J Cancer Prev, **27 (8)**, 2831-2837

Introduction

The 22-member human apolipoprotein (*APO*) gene family encodes apolipoproteins with diverse biological functions, including lipid binding and transport, regulation of specific lipases, receptor binding and signaling, and control of the expression of specific genes [1]. Mutations and dysregulation of *APO* genes lead to metabolic diseases such as hyperlipidemia, atherosclerosis, and coronary artery disease [1, 2]. Recent data suggest that several apolipoprotein genes, including the *APOB* gene, are associated with cancer of diverse organs, including the liver, gall bladder, colon, breast, and prostate [2, 3]. The *APOB* gene (2P24.1) encodes two proteins, *APOB*-48 and *APOB*-100. *APOB*-48 is expressed in the intestine. It binds and transports absorbed dietary lipids, as well as vitamins A and E. *APOB*-100 is expressed in the liver and many other organs. *APOB*-100 is a key component of very low-density, low-density, and intermediate-density lipoprotein particles. These particles move through the bloodstream, transporting lipids to cells via *APOB*-100 (and APOE) binding to specific cellular receptors [4]. Many apolipoprotein genes, including *APOB*, are polymorphic (have seemingly benign mutations at frequencies>1.0%). Some of the polymorphisms are associated with various pathologies, including cancers [1]. This study examines the association between single-nucleotide polymorphisms (SNPs) rs693 and rs1042031 of the *APOB* gene and the risk of prostate diseases.

Materials and Methods

Patients and control subjects

Subjects in this study participated in a prostatic disease screening event organized by Professor Asmahan El Ezzi and Wissam Zaidan in collaboration with hospitals and

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clinics in Lebanon. The subjects (50 years in age or older at the time) provided informed consent to donate a blood sample, participate in prostate-specific antigen (PSA) screening, and permit the extraction and use of DNA for genetic analysis and research. A urologist evaluated each participant's prostate health and serum total PSA (PSA-T) levels, followed by a digital rectal examination (DRE) if necessary. PSA-T levels were measured using immunoassay (Immunotech, Marseille, France). A free PSA test (PSA-F) was performed for subjects with PSA-T levels between 3 and 10 ng/ml (the gray zone), and the PSA F/T ratio was calculated to help differentiate between BPH and PCa. The International Prostate Symptom Score (IPSS) was also evaluated, and transrectal ultrasonography was performed when necessary. Subjects were placed in the control group if they had normal PSA levels for two consecutive years, a normal IPSS score, and a normal DRE at the time of blood sampling. The study included 59 subjects with confirmed PCa, 55 subjects with confirmed BPH, and 63 controls with no prostatic disease.

Ethical statement

Consent of each participant was obtained in accordance with the ethical standards outlined in the 1975 Declaration of Helsinki [5]. The present study (genetic study using leftover DNA samples) received approval from the Institutional Review Board (IRB) of Utah Valley University (IRB approval #1013).

Molecular methods

DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (QIAGEN, Milan, Italy). DNA samples were genotyped using the Polymerase Chain Reaction- Restriction Fragment-Length Polymorphism (PCR-RFLP) method. Briefly, a DNA fragment flanking the SNP was PCR-amplified, the amplified fragments were digested with a restriction endonuclease (RE), and then resolved on a gel by electrophoresis. The SNP genotypes were scored based on the band patterns. The primers used for the SNP rs693 (7673 C/T) were 5'CAGCTTAAGAGACACATAC3' and 5'CTACCAATGCTTTCATACG3', and that for rs1042031 (12669 G/A) were 5'CGGGAATCTGATGAGGAAAC3' and 5'CAGTTCCCTATACATCGAG'3' [6]. The PCR mixture (15 µl) contained 1x reaction buffer (containing 0.75 units of Taq DNA polymerase) (QIAGEN, Germantown, MD), 10 picomoles of each primer, and 10 ng of template DNA. Negative controls contained the same components except for the template DNA. PCR amplification was performed using a GeneAmp 2700 thermocycler (Applied Biosystems, Carlsbad, CA) with the following program: 94°C for 5 minutes (one cycle), then 94°C for 45 seconds, 56°C for 45 seconds, 72°C for 45 seconds (35 cycles); followed by 72°C for 5 minutes (one cycle), then a soak at 4 °C. To prevent cross-contamination, the PCR mixture was prepared in a UV-decontaminated Class IIA2 biosafety cabinet equipped with a HEPA filter, using dedicated pipettes. Amplified PCR products were analyzed in a separate space from where the PCR setup was done. The authenticity of the amplicons was confirmed by size and restriction mapping (for rs693, HinDIII, and for rs1042031, BbsI digestion).

For genotyping, the amplicon for rs693 (943 bp) was digested with XbaI (5'TCTAGA3') (NEB, Beverly, MA) and that for rs1042031 (681 bp) was digested with EcoRI (5'GAATTC3') (NEB), using 0.2 units, at 37 °C, overnight) and then resolved in 5-6 % polyacrylamide vertical gel for 90 minutes at 10 volts/cm using 0.5x Tris-borate-EDTA buffer. The gel was stained with ethidium bromide (0.5 µg/mL) for 30 minutes and then digitally documented on a UV transilluminator. By convention, the allele having the restriction site was considered recessive. For rs693 C>T transition, the C allele allows the XbaI (5'TCTAGA3') digestion (thus, X=T, x=C). For rs1042031 G>A transition, the G allele allows EcoRI (5'GAATTC3') digestion (thus, E=A, e=G). The alleles are indicated as X or x and E or e throughout this article. Since RFLP was used for genotyping, haplotype analysis was limited to homozygotes for both alleles. For example, the haplotype of an individual with genotypes XX and EE is XE.

Statistical analyses

The frequencies of genotypes for the SNPs in the three sample groups were analyzed alongside Hardy-Weinberg (H-W) equilibrium using the χ^2 goodness-of-fit test. The null hypothesis that the genotypes of the three populations are in H-W equilibrium was rejected if the calculated $\chi 2$ test statistic produced a p-value <0.05. The association between each polymorphic genotype of the SNP and PCa and BPH was assessed by calculating the odds ratio (OR) and the 95% confidence interval (CI). A p-value < 0.05 was considered statistically significant. The OR, RR, 95% CI, and p-values were calculated using MedCalc Statistical Software (MedCalc, Ostend, Belgium).

Results

Distribution of genotypes

Distribution of the homozygous dominant, homozygous recessive, and heterozygous genotypes in the three groups is shown in Table 1. The groups conformed to the Hardy-Weinberg equilibrium, except for the controls for both SNPs, and the PCa and the affected (i.e., PCa+BPH) group for rs1042031 (Table 1).

Distribution of allele frequency

The frequency of the rs693 alleles X and x was not significantly different between the control and the PCa group (p=0.09). However, the X allele was significantly more prevalent in the BPH group (p=0.03) and the combined affected (PCa + BPH) group (p = 0.02) compared to the control group (Table 2), indicating a possible association of the X allele with the risk of prostatic diseases.

The frequency of the rs1042031 allele E was significantly higher in the PCa group compared to the control group (p = 0.03). However, the frequency of the E and e alleles was not significantly different for the BPH group (p=0.19) and the combined affected (PCa+BPH) group (p=0.37), compared to the control group (Table 2). This data indicates a possible association between the E

Table 1. The Difference between the Observed and Expected Ratios of the Different Genotypes for the SNP rs693 (C/T transition) and rs1042031 (A/G transition) of the *APOB* Gene in the Control and Affected Groups

Sample	Observed			Expected			χ^2
Locus XbaI	XX	Xx	xx	XX	Xx	xx	
Control	25	12	26	15.25	31.49	16.25	24.14*
PCa	23	25	11	21.36	28.28	9.36	0.79
BPH	21	28	6	22.27	25.45	7.27	0.55
PCa+BPH	44	53	17	43.6	53.8	16.6	0.03
Locus EcoRI	EE	Ee	ee	EE	Ee	ee	
Control	0	38	25	5.73	26.54	30.73	11.75*
PCa	6	39	14	11.02	28.96	19.02	7.10*
BPH	5	32	18	8.02	25.96	21.02	2.97
PCa+BPH	11	71	32	18.97	55.07	39.97	9.55*

* Significant at 0.05 level

allele and the risk of PCa but not with BPH.

Distribution of genotypic ratios

The distribution of the ratios of different genotype combinations for the three groups is shown in Table 3. For rs693, the ratios of the following combinations were significantly different between the control and the PCa group: Xx/(XX+xx) (p=0.006) and xx/(XX+Xx) (p=0.008); the control and BPH group: XX/xx (p=0.017), XX/Xx (p=0.025), and Xx/(XX+xx) (p=<0.001) and xx/(XX+Xx) (p=<0.001); the control and the affected (PCa+BPH) group: XX/xx (p=0.013), XX/Xx (p=0.024), Xx/(XX+xx) (p=0.001) and xx/(XX+Xx) (p=<0.001) (Table 3), indicating that a possible association of the X allele with the risk of prostatic diseases.

For rs1042031, the ratios of the following combinations were significantly different between the control and the PCa group: EE/ee (p=0.038); the control and the affected (PCa+BPH) group: EE/ee (p=0.049) (Table 3), indicating a possible association between the E allele and risk of prostatic diseases (Table 3).

Genotype combinations and haplotype ratios

The distribution of risk-associated genotypes (i.e., genotypes with the X and E alleles) and risk-free genotypes (i.e., genotypes with the x and e alleles) in the control and affected groups is shown in Table 4. Compared to the control group, the ratio of (XX+ EE)/(xx+ee), and

Table 2. The Difference in the Frequency of the Alleles for the SNP rs693 (C/T transition) and rs1042031 (A/G transition) of the *APOB* Gene in the Control and Affected Groups

Alleles	Control	Affected	OR	95% CI	p-value
SNP rs693 (C/T)					
Control vs. PCa					
X	62 (0.49)	71 (0.60)	1	0.94-2.59	0.09
x	64 (0.51)	47 (0.40)	1.56		
Control vs. BPH					
X	62 (0.49)	70 (0.64)	1	1.07-3.05	0.03*
x	64 (0.51)	40 (0.36)	1.8		
Control vs. (PCa+BPH)					
X	62 (0.49)	141 (0.62)	1	1.08-2.60	0.02*
x	64 (0.51)	87 (0.38)	1.67		
rs1042031(A/G)					
Control vs. PCa					
E	38 (0.30)	51 (0.43)	1	1.04-2.98	0.03*
e	88 (0.70)	67 (0.57)	1.76		
Control vs. BPH					
E	38 (0.30)	42 (0.38)	1	0.83-2.46	0.19
e	88 (0.70)	68 (0.62)	1.43		
Control vs. (PCa+BPH)					
E	38 (0.30)	93 (0.41)	1	0.78-1.94	0.37
e	88 (0.70)	175 (0.59)	1.23		

*, Significant at the 0.05 level

Table 3. Differences in the Ratios of Different Genotype Combinations for SNP rs693 (C/T transition) and rs1042031 (A/G transition) of the *APOB* Gene in the Control and Affected Groups

Allele ratio	Control	Affected	OR	95% CI	p-value
SNP rs693: Control vs. PCA					
XX/xx	25/26	23/11	2.17	0.88, 5.37	0.092
XX/Xx	25/12	23/25	0.44	0.18, 1.08	0.072
XX/(Xx+xx)	25/38	23/36	0.97	0.47, 2.01	0.94
Xx/(XX+xx)	12/51	25/34	3.13	1.39, 7.05	0.006*
xx/(XX+Xx)	26/37	11/48	0.33	0.14, 0.74	0.008*
SNP rs693: Control vs. BPH					
XX/xx	25/26	21/6	3.64	1.26, 10.51	0.017*
XX/Xx	25/12	21/28	0.36	0.45, 1.97	0.025*
XX/(Xx+xx)	25/38	21/34	0.94	0.45, 1.97	0.167
Xx/(XX+xx)	12/51	28/27	4.41	1.94, 10.02	0.000*
xx/(XX+Xx)	26/37	6/49	0.17	0.07, 0.47	0.000*
SNP rs693: Control vs. affected (PCa+BPH)					
XX/xx	25/26	44/17	2.69	1.23, 5.90	0.013*
XX/Xx	25/12	44/53	0.4	0.18, 0.88	0.024*
XX/(Xx+xx)	25/38	44/70	0.96	0.51, 1.79	0.887
Xx/(XX+xx)	12/51	53/61	3.69	1.78, 7.65	0.000*
xx/(XX+Xx)	26/37	17/97	0.25	0.12, 0.51	0.000*
SNP 1042031: Control vs. PCA					
EE/ee	0/25	6/(14)	22.86	1.99, 435.88	0.038*
EE/Ee	0/38	6/(39)	12.67	0.69, 232.72	0.087
EE/(Ee+ee)	0/63	6/(53)	15.43	0.85, 280.26	0.064
Ee/(EE+ee)	38/25	39/20	1.28	0.61, 2.68	0.509
ee/(EE+Ee)	25/38	14/45	0.47	0.21, 1.04	0.061
SNP 1042031: Control vs. BPH					
EE/ee	0/25	5/(18)	15.16	0.79, 291.53	0.072
EE/Ee	0/38	5/(32)	13.03	0.69, 244.65	0.086
EE/(Ee+ee)	0/63	5/(50)	13.83	0.75, 256.10	0.078
Ee/(EE+ee)	38/25	32/23	0.92	0.44, 1.91	0.81
ee/(EE+Ee)	25/38	18/37	0.74	0.35, 1.58	0.434
Control vs. affected (PCa+BPH)					
EE/ee	0/25	11/(32)	18.05	1.05, 331.02	0.047*
EE/Ee	0/38	11/(71)	12.38	0.71, 215.92	0.084
EE/(Ee+ee)	0/63	11/(103)	14.11	0.81, 243.62	0.069
Ee/(EE+ee)	38/25	71/43	1.09	0.58, 2.04	0.78
ee/(EE+Ee)	25/38	32/82	0.59	0.31, 1.14	0.115

*Significant at 0.05 level

(XX+Xx+EE+Ee)/(xx+ee) is significantly higher in PCa group (p=0.019 and 0.001, respectively), in the BPH group (p=0.033 and 0.002, respectively), and in the combined (PCa+BPH) affected group (p=0.008 and <0.001, respectively). The (XX+EE)/(Xx+xx+Ee+ee) ratio of the control and the affected groups was not statistically significant (Table 4).

Since RFLP was applied for genotyping, haplotypes were determined only for individuals homozygous for both alleles. The haplotypes are the following: Control group: XE= 0, Xe= 6, xe=9; PCa group: XE= 2, Xe= 5, xe=0; and BPH group: XE= 2, Xe= 8, xe=0. Applying the chi-square test with 4 degrees of freedom, we obtained a p-value of 0.0009, indicating an association of the XE haplotype with the risk of prostatic diseases and a lack of association for the Xe and xe haplotypes.

Discussion

The genetic polymorphism of the *APOB* gene was initially reported in 1986, based on the binding of monoclonal antibodies to apolipoprotein B proteins [7]. The dbSNP database [8] currently lists some 75 verified SNPs in the 42.6 kb *APOB* gene, which contains 29 exons

Table 4. Differences in the Ratios of Risk-Associated and Other Genotype Combinations for SNP rs693 (C/T transition) and rs1042031 (A/G transition) of the *APOB* Gene in the Control and Affected Groups

Combination of genotypes	Control	Affected	OR	95% CI	p-value
Control vs. PCa					
(XX+EE)/(xx+ee)	25/51	29/25	2.37	1.15, 4.85	0.019*
(XX+EE)/(Xx+xx+Ee+ee)	25/101	29/89	1.32	0.72, 2.41	0.37
(XX+Xx+EE+Ee)/(xx+ee)	75/51	93/25	2.52	1.43, 4.46	0.001*
Control vs BPH					
(XX+EE)/(xx+ee)	25/51	26/24	2.21	1.06, 4.60	0.034*
(XX+EE)/(Xx+xx+Ee+ee)	25/101	26/84	1.25	0.67, 2.33	0.48
(XX+Xx+EE+Ee)/(xx+ee)	75/51	86/24	2.43	1.37, 4.33	0.002*
Control vs. PCa+ BPH					
(XX+EE)/(xx+ee)	25/51	55/49	2.29	1.24, 4.23	0.008*
(XX+EE)/(Xx+xx+Ee+ee)	25/101	55/173	1.28	0.75, 2.19	0.36
(XX+Xx+EE+Ee)/(xx+ee)	75/51	179/49	2.48	1.54, 3.40	0.000*

* Significant at the 0.05 level

and 28 introns. Some of these SNPs are associated with the risk of diseases, including cancer [1]. The SNPs rs693 and rs1042031 are in exons 26 and 29 of the gene, respectively. The SNP rs693 C/T transition affects a single codon, resulting in a glutamine-to-arginine substitution. In contrast, the rs1042031 A/G transition is a silent mutation without any change in the codon [9]. Both mutations may also affect the overall expression of the gene, influencing various processes, including pre-mRNA processing, transport, stability, and the rate of mRNA translation [10]. Several reports have indicated an association between the SNPs rs693 and rs1042031 and lipid metabolism, as well as body mass index [11-13]. Liu et al. examined the relationship between these two SNPs and breast cancer in China [6]. To our knowledge, the present report is the first to investigate the association between these two polymorphisms and prostate diseases among older males in Lebanon.

Lebanon has approximately 0.65 million males aged 50 years or older [14]. With an average male life expectancy of 77.8 years, a tobacco use rate of 47.5%, an obesity rate of 32%, alcohol consumption of 1.14 liters per person per year, and exposure to various pollutants, including 24.23 micrograms per cubic meter of particulate air pollutants [15], cancer presents a significant public health concern for the older male population in Lebanon. In 2015 (the latest reporting year), PCa (31.17/100,000) was the most common cancer among Lebanese men [15]. In 2021, the latest reporting year, Safiri et al. [16] reported that the age-standardized prevalence rate of BPH in Lebanon was 2151 per 100,000, representing a 4.6% increase since 1990. The small male population in the target age group and low participation rates in the screening event allowed us to have a relatively small sample size. The genotypic ratios for the two SNPs (Table 1) yielded mixed results, with four of the eight samples showing conformity to the Hardy-Weinberg equilibrium, indicating an adequate sample size for both genetic and epidemiological studies [17, 18]. The lack of conformity with the Hardy-Weinberg equilibrium for the other four samples indicates a sample-size limitation of this study.

In this study, the distribution of the allele frequency indicated an association of the X (i.e., the T) allele of the SNP rs693 with BPH (p=0.02), the combined (PCa+BPH) prostatic diseases (p=0.02), and possibly PCa (p=0.09), and the E (i.e., the A) allele of rs1042031 with BPH (p=0.03) but not with PCA (p=0.19) and combined (PCa+BPH) prostatic diseases (p=0.37) (Table 2). However, an analysis of the variations in the ratio of various genotypes in the control and affected groups indicated a strong association between the X allele of rs693 and the E allele of rs1042031 with prostate disease (Table 3). Further analysis of the differences in the ratio of various combination genotypes for both rs693 and rs1042031 SNPs confirmed an association between the X and E alleles and prostate disease (Table 4). Our limited data on haplotype analysis indicate that the GE haplotype is associated with an increased risk of prostate disease, whereas Xe and xe haplotypes are not.

The SNP rs693 had been previously implicated in other cancers. For example, Liu et al. [6] reported an association between the X allele of the SNP rs693 and the E allele of rs104203, both of which are associated with an increased risk of breast cancer in the Chinese population. Another report indicated an association of the X- (i.e., the T) allele with increased risk of gallbladder cancer [19]. However, Baez et al. [20] observed that the T/T genotype of the SNP is associated with reduced risk of gallbladder cancer, and Pandey et al. [21] found no significant association of the SNP with the risk of gallbladder cancer. A meta-analysis [22] found that the X+/X+ (i.e., the CC) genotype is associated with a decreased risk of gallbladder cancer. Overall, it appears that the X allele is associated with increased risk of some cancers. The association of the X allele of the SNP rs693 and the E allele of the SNP rs1042031with increased risk of PCa and breast cancer may be biologically relevant. Both the breast and the prostate are lipid-rich and steroid hormone-sensitive organs. In addition, both breast and prostate cancers are cancers of epithelial cells, and both cancer types are gonadal hormone-dependent, having many underlying biological similarities [23]. Further studies are warranted

to examine if these polymorphisms of the *APOB* gene are associated with cancer of other organs.

Our repeated online search found no published report on the association of the two SNPs of the *APOB* gene and the risk of BPH. BPH is not neoplastic; it results from the proliferation of epithelial and stromal cells and responds to gonadal hormones [24]. BPH is not considered a risk factor for PCa [25], although this proposition has been recently challenged [26]. Both PCa and BPH share some common risk factors and benefit from some similar therapeutic interventions [26, 27]. Since, unlike PCa, BPH exhibits disease signs early in the disease's progression, genetic markers associated with BPH can aid in early diagnosis and intervention to prevent PCa. Such high-penetrance genetic markers have yet to be identified, but some progress has been made [26].

Although the present and previously reported data [6] suggest that the X allele of rs693 and the E allele of the SNP rs1042031 are associated with an increased risk of cancer, further studies are necessary to validate these findings. Several factors, including polygenic inheritance, penetrance, epistasis, and diverse environmental influences on different populations [28], may contribute to clinical outcomes. Since complex traits are generally polygenic and most genes are polymorphic [29], every individual carries a mixture of risk-associated and protective alleles. It makes the identification of high-penetrance markers difficult. A systems biology approach, such as the genome-wide association studies (GWAS), is currently being applied to address the issue [30]. However, identifying critical genetic polymorphisms associated with disease risk across diverse ethnic groups will remain valuable for the discovery and validation of genetic markers.

We used leftover DNA samples from a screening campaign that had limited access to the pathological and other patient information, which is a limitation of this study. We plan to investigate the apolipoprotein profile of subjects with prostatic diseases and compare it to that of their healthy counterpart.

In conclusion, this data confirms and expands on previous findings regarding the association of the SNPs rs693C>T (i.e., the X allele) and rs1042031G>A (i.e., the E allele), and the XE haplotype of the *APOB* gene with an increased risk of prostatic diseases. This is the first report on the association of the X allele of SNP rs693C and the E allele of SNP rs1042031 with an increased risk of PCa and BPH. Given the small sample size (n=177), the generalizability of these findings is limited, although a small sample size is not considered a severe limitation for epidemiological and genetic analyses [17, 18]. Our results provide meaningful insights into the complexity of interactions among diverse genes and prostate health, encouraging other researchers to replicate this study with larger, more diverse sample sizes. These findings need to be validated by further studies, including larger association studies such as GWAS, and functional studies. Additional studies are warranted to investigate if these and other SNPs of the *APOB* gene are associated with other cancers.

Author Contribution Statement

Conception: Asmahan A. El Ezzi and Ruhul H. Kuddus; Blood sampling, data recording, PSA testing, DNA extraction, and patient follow-up: Asmahan El Ezzi and Wissam Zaidan; Genetic data acquisition and funding: Brock Sheehan, Connor Dority, Keante Springle, Joshua George, and Ruhul Kuddus; Data analysis and Interpretation: Mohammed A. El-Saidi, Brock Sheehan, and Ruhul Kuddus; Supervision: Asmahan A. El Ezzi and Ruhul H. Kuddus; Manuscript preparation: Ruhul Kuddus (all authors reviewed, corrected, and approved the final manuscript).

Acknowledgements

The Undergraduate Cancer and Public Health Research Initiative sponsored this work. The authors thank Ms. Hassana Shouman for data entry and Drs. Nabil Al-Ahmadieh and Kalim Hraiki for their invaluable help in the early stages of this project.

Funding

Funded internally by Utah Valley University (SAC Grant DTRS07).

Approval

Institutional Review Board (IRB) of Utah Valley University (IRB approval #1013).

Data Availability

Data are available upon request from the corresponding author.

Conflict of Interest

The authors had nothing to disclose.

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