

## SRD5A2 Polymorphisms and Risk of Prostate Cancer in Men with Benign Prostate Hyperplasia

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**Abstract.** Prostate cancer (PRCa) is one of the most common causes of cancer death in men and determinants of PRCa risk remain largely unidentified. This study design to assess the predictive value of three polymorphisms in *SRD5A2* to determine the risk of developing PRCa in patients with benign prostatic hyperplasia (BPH). The study evaluated 28 patients who presented with PRCa at least 6 years after the diagnosis of BPH and 56 matched patients with BPH who did not progress to PRCa over a comparable period. Polymorphisms *V89L* and *A49T* were detected by RFLP analysis and The  $(TA)_n$  repeats was determined using an ABI PRISM 310 Genetic analyser. BPH patients with  $(TA)_0$  allele of the  $(TA)_n$  marker had statistically no significant risk of developing PRCa (OR: 3.24, 95% CI= 0.37-28.33) compared with BPH patients with  $(TA)_9$  allele. For the *V89L* marker, The OR for risk of developing PRCa was 1.29 (95% CI= 0.69-2.40) in BPH patients having a *V* allele. The frequency of the *A49T TT* genotype was higher in cases (7%) compared to control subjects (2%), although this was not statistically significant (OR=1.3, 95% CI=0.55-3.10). This is the first study effort to examine the role of *SRD5A2* polymorphisms (*V89L*, *A49T* and  $(TA)_n$ ) in the development of PRCa in patients with BPH. Although this study found no statistically significant association of these three polymorphic markers with PRCa risk in BPH patients, a modest effect can not be ruled out.

**Key word:** 5  $\alpha$ -reductase, SRD5A2, prostate cancer, polymorphism, benign prostate hyperplasia, PRCa, BPH.

### Introduction

Prostate cancer (PRCa) constitutes a major health issue worldwide (Parker *et al.*, 1996; Prior and Waxman 2000). The aetiology of PRCa is unclear, although current evidence suggests that PRCa is the result of multiple factors that include ethnicity, environmental, genetics, hormonal and dietary factors (Holund 1980; Whittemore *et al.*, 1995; Pienta *et al.*, 1996; Wingo *et al.*, 1996; Hsieh *et al.*, 1999; Tzonou *et al.*, 1999). Benign prostatic hyperplasia (BPH) is a non-neoplastic enlargement of the prostate. BPH is extremely common, with a rapid increase in prevalence in the fourth decade of life. According to epidemiological studies most cancers are associated with BPH elsewhere in the prostate (83.3%) (Carter and Coffey 1990; Bostwick *et al.*, 1992) and approximately 3-20% of patients who have undergone transurethral prostatectomy (TURP) or open prostatectomy for BPH subsequently develop PRCa (Armenian *et al.*,

1974; Schwartz *et al.*, 1986; Bostwick *et al.*, 1992). Compared to men without BPH, those with the condition have a five-fold raised risk of developing PRCa and a four-fold raised risk of death from PRCa (Armenian *et al.*, 1974). A previous study reported that a family history of prostate disease (PRCa or BPH) was more frequently seen in relatives of men with BPH (20%) than in relatives of men with PRCa (12.8%) or in healthy controls (5.1%) (Schuman *et al.*, 1977). In addition, *in vitro* malignant transformation of BPH tissue has been previously reported (Chen and Heidelberger 1969; Fraley *et al.*, 1970; Franks and Wilson 1970). These results suggest that common genetic mechanisms may predispose to benign and malignant prostate disease. Moreover these results suggest that BPH may be part of a premalignant environment condition in the prostate gland. With the increasing incidence of PRCa in many populations there is an urgent need for the identification of molecular

markers that can serve as indicators of disease risk to focus chemoprevention and early detection strategies. Human prostatic steroid 5 $\alpha$ -reductase, is encoded by the *SRD5A2* gene catalyses the irreversible conversion of testosterone to 5 $\alpha$ -dihydrotestosterone (DHT), the most potent androgen in the prostate. It has been proposed that increased activity of this enzyme may lead to PRCa susceptibility and/or aggressiveness (Makridakis et al., 2000). Japanese men, with one of the lowest incidence rates of PRCa, have reduced activity of 5 $\alpha$ -reductase (Ross et al., 1992). *SRD5A2* gene located on the 2p23 and variation in the *SRD5A2* may have an effect on predisposition to PRCa (Labrie et al., 1992; Thigpen et al., 1992). Different polymorphisms in the *SRD5A2* were identified and their relations with the risk of PRCa were determined. The first polymorphism was (*TA*)<sub>n</sub> dinucleotide repeat in the 3' UTR of the gene. A previous study found differences in the distribution of this polymorphic repeat in different ethnic groups (Reichardt et al., 1995). However, other studies found a weak or no association between this polymorphism and risk of PRCa (Kantoff et al., 1997; Lamharzi et al., 2003; Ntais et al., 2003). Other polymorphisms in the *SRD5A2* includes the missense substitution (*V89L*) which showed no association with risk of PRCa (Davis and Russell 1993; Lamharzi et al., 2003; Ntais et al., 2003; Makridakis et al., 1999) and the *A49T* missense substitution in exon 1 of the gene, which showed a significant association with the risk of PRCa in African American and Hispanic men (Makridakis et al., 1999). Moreover, results from previous study demonstrated that the *A49T* variant lead to an increase 5 $\alpha$ -reductase activity and circulating level of DHT (Makridakis et al., 1999; Allen et al., 2003).

This study determined if polymorphisms (*V89L*, *A49T* and (*TA*)<sub>n</sub>) of the *SRD5A2* were related to risk of developing PRCa in patients with BPH.

## Material and Methods

### Study population

This study took advantage of a comprehensive population-based health care system to identify a well-defined case-control study nested within a cohort with BPH. The initial data set contained 11,606 BPH biopsies representing all histologically proven cases of this disease in Northeast Scotland (Grampian region)

from 1974-1990. A total of 1896 patients had more than 1 prostate biopsy during this time period and cases and control were selected from within this group. Cases were patients with only BPH in the initial biopsy and a second biopsy with PRCa obtained  $\geq 6$  years after the BPH biopsy. Paraffin-embedded tissue samples were obtained from 28 cases; the PRCa was diagnosed between 6 and 15 years after the initial BPH sample. Two controls were matched to each case on age and year of BPH diagnosis. Controls which had biopsy proven evidence of a benign prostate  $\geq 6$  years (range 6-15 years) after the initial BPH procedure. All cases and controls were Caucasian, thus guarding against the effects of population stratification. All sections were rereviewed by two pathologists to confirm the diagnosis. While these strict selection procedures substantially reduced the number of subjects available for evaluation, it produced a powerful data set for detection of factors that predispose patients with BPH to the development of PRCa.

### DNA extraction

DNA was extracted from formalin fixed, paraffin-embedded tissues. The tissue sections were deparaffinized with xylene and ethanol and then DNA was isolated by proteinase K digestion (Frank et al., 1996).

### PCR assay

PCR primers were designed to amplify a fragment around the *SRD5A2* (*TA*)<sub>n</sub> repeat (forward primer 5'-GCT GAT GAA AAA CTG TCA AGC TGC TGA-3' and reverse primer 5' TET -GCC AGC TGG CAG AAC GCC AGG AGA C-3'). Previously described primer sets were used to amplify regions around the *V89L* & *A49T* polymorphisms (Jaffe et al., 1999). Genomic DNA (100-500 ng) was subjected to PCR amplification in a 25  $\mu$ l reaction mixture containing 10 $\times$  PCR buffer (MBI, Sunderland, UK), 1mM MgCl<sub>2</sub> (MBI), 200  $\mu$ M dNTP mix (Bioline, London, UK), 10 pmol of each primer, 1 unit of Taq polymerase (Roche, Lewes, UK), and sterilized distilled water. The genomic DNA was initially denatured at 94  $^{\circ}$ C for 2 min and thereafter subjected to 35 cycles of PCR amplification with denaturation for 1 min at 94  $^{\circ}$ C, annealing for 2 min at 60  $^{\circ}$ C, extension for 2 min 30 sec at 72  $^{\circ}$ C, and final extension at 72  $^{\circ}$ C for 10 min.

### Genotype analysis

The size of PCR products and repeats number for *SRD5A2* ( $(TA)_n$ ) was determined using an ABI PRISM 310 (automated fluorescent capillary electrophoresis system) Genetic analyser (Perkin Elmer, Applied Biosystems, Warrington, UK). The reproducibility with which the repeat size could be determined was estimated by comparison of samples between different ABI-310 runs. In each case, both the PCR amplification and the ABI-310 analysis were repeated at least twice.

The *V89L* & *A49T* variants were determined by digestion of the PCR products with the restriction endonuclease *RsaI* and *MwoI* respectively. Genotypes for the two SNPs were determined after separation on a 4% Metaphor. Digestion of the PCR products with the *RsaI* produced 169, 105, 64, and 19 bp fragments corresponding to the *V* allele, and 169, 105, and 83 bp fragments corresponding to the *L* allele. Digestion of the PCR products with the *MwoI* produced 90, 70, 46/47, and 17/20/21/22 bp fragments corresponding to the *A* allele, and 107, 70, 46/47, and 20/21/22 bp fragments corresponding to the *T* allele.

### Statistical analysis

The distribution of *V89L*, *A49T* and  $(TA)_n$  genotypes in the cases and controls, were compared with that expected from the Hardy-Weinberg equation and with each other using the Chi-squared test. Conditional logistic regression methods were used, in STATA (StataCorp, 1999), to compute odds ratios (OR) for PRCa risk, and 95% confidence intervals (CI), associated with each genotype.

### Results

*Distribution of  $(TA)_n$  Genotype and allele frequencies in case, control populations* Fragment analysis of the 3' UTR of the *SRD5A2* gene using the outlined methodology distinguishes three genotypes:  $(TA)_0$  (no repeats present),  $(TA)_0/(TA)_9$ , and  $(TA)_9$  (nine *TA* repeats) (Table 1).  $(TA)_{18}$  repeat lengths were not detected in any of the samples in the present study (Table 1). The  $(TA)_0$  allele was the most common allele of the  $(TA)_n$  repeat polymorphism, and the  $(TA)_9$  allele was found to be less common among cases than controls (0.02 and 0.06 respectively, Table 1). No statistically significant difference for  $(TA)_0$  allele

distribution ( $P=0.264$ , OR: 3.24, 95% CI= 0.37-28.33) was found in the study groups.

### *Distribution of V89L & A49T Genotype and allele frequencies in case, control populations*

The results of *V89L* genotype analysis showed a high frequency of the *VV* genotype in BPH patients who subsequently developed PRCa (Table 2). However the results was not statistically significant ( $P=0.807$ ; Table 2). The OR for risk of developing PRCa was 1.29 (95% CI= 0.69-2.40) in BPH patients having a *V* allele. *V89L* genotype frequency in the cases and controls showed no significant differences from that expected from Hardy-Weinberg equilibrium.

A similar pattern was seen for *A49T*, where the *TT* genotype was overrepresented in the cases compared to the controls (Table 2), although risk was not statistically significantly raised ( $P=0.807$ ). The OR for risk of developing PRCa was 1.3 (95% CI= 0.55-3.10) in BPH patients having a *T* allele. *A49T* genotype frequency in the cases and controls showed no significant differences from that expected from Hardy-Weinberg equilibrium.

### Discussion

PRCa is one of the most commonly diagnosed cancers in men. Previous studies have defined a significant association between BPH and developing PRCa (Armenian *et al.*, 1974; and 1975; Mishina *et al.*, 1985). With the increasing incidence of BPH in the ageing population, identification of risk factors for development of PRCa in BPH patient is an urgent necessity. Germline variation in genes directly involved in regulation of prostate cell proliferation and differentiation might be critically important in understanding carcinogenesis event of PRCa, as these variants might be used as a diagnostic, prevention, and prognostic markers for PRCa. If molecular markers in patients with BPH are shown to be predictors of eventual malignant transformation, then more intensive surveillance and/or early treatment could be offered to those carrying the markers of high-risk. In the converse situation, those patients who do not have a high risk of malignant transformation could be offered standard follow-up monitoring. In our previous studies we reported that a *CYP3A4*, *VDR* variant alleles and *AR* mosaicism are associated with

**Table 1.** Distribution of SRD5A2 (TA)<sub>n</sub> genotype and allele frequencies in case, control populations. n = number of subjects, (%)

Population		Genotype frequency							Allele Frequency	
		<i>TA</i> <sub>0</sub> / <i>TA</i> <sub>0</sub>	<i>TA</i> <sub>0</sub> / <i>TA</i> <sub>9</sub>	<i>TA</i> <sub>0</sub> / <i>TA</i> <sub>18</sub>	<i>TA</i> <sub>9</sub> / <i>TA</i> <sub>9</sub>	<i>TA</i> <sub>0</sub> / <i>TA</i> <sub>18</sub>	<i>TA</i> <sub>18</sub> / <i>TA</i> <sub>18</sub>	<i>TA</i> <sub>0</sub>	<i>TA</i> <sub>9</sub>	<i>TA</i> <sub>18</sub>
Case	28	27 (96%)	1 (4%)	0 (0)	0 (0)	0 (0)	0 (0)	0.98	0.02	0
Control	56	50 (89%)	5 (9%)	0 (0)	1 (2%)	0 (0)	0 (0)	0.94	0.06	0

**Table 2.** Distribution of SRD5A2 V89L & A49T genotype and allele frequencies in case, control populations. n = number of subjects, (%)

Population		Genotype frequency			Allele Frequency		Genotype frequency		Allele Frequency		
		<i>VV</i>	<i>VL</i>	<i>LL</i>	<i>V</i>	<i>L</i>	<i>AA</i>	<i>AT</i>	<i>TT</i>	<i>A</i>	<i>T</i>
Case	28	17 (61)	8 (28)	3 (11)	0.75	0.25	20 (71)	6 (21)	2 (7)	0.82	0.18
Control	56	30 (54)	18 (32)	8 (14)	0.70	0.30	41 (73)	14 (25)	1 (2)	0.86	0.14

a group of men with BPH that are at an increased risk of PRCa and might be a useful component of a polygenic prediction strategy for this important disease (Tayeb *et al.*, 2002; Tayeb *et al.*, 2003; Tayeb *et al.*, 2004; Tayeb *et al.*, 2004). The role of the SRD5A2 enzyme in PRCa is evident from biological and epidemiological studies. Androgens are known to play an important role in PRCa development and progression, and SRD5A2 may be involved through increased production of DHT (Bharaj *et al.*, 2000). This study has investigated three polymorphisms in the SRD5A2 gene and risk of PRCa in the patients with BPH. This study found no statistically significant associations with PRCa risk the (*TA*)<sub>0</sub> V89L and A49T polymorphisms in the SRD5A2 gene, although a modest effect of these markers cannot be ruled out. Because the (*TA*)<sub>n</sub> marker is located in the 3' UTR of the SRD5A2 gene, its functional consequences are thought to be due to the instability of mRNA transcripts with UA-rich 3' UTRs (transcribed from TA-rich regions of DNA (Zubiaga *et al.*, 1995; Makridakis *et al.*, 1999) which may in turn affect 5-reductase activity levels. Three major (*TA*)<sub>n</sub> alleles have been reported, namely, (*TA*)<sub>0</sub> (*TA*)<sub>9</sub> and (*TA*)<sub>18</sub> with (*TA*)<sub>0</sub> being the most common in most populations. In this study, 96% and 86% of the case and controls had the (*TA*)<sub>0</sub> (*TA*)<sub>0</sub> genotype respectively. Consistence with previous study (Kantoff *et al.*, 1997), this study found that men carrying copies of the (*TA*)<sub>0</sub> allele had

a no significantly higher risk o PRCa. The results of this study confirm previous finding of the rarity of (*TA*)<sub>18</sub> as this allele could not be determined in this study (Bharaj *et al.*, 2000). Of the more than 20 polymorphisms reported for the SRD5A2 gene, V89L is the most common (Makridakis *et al.*, 1999). Consistence with the previous studies we found a higher risk of developing PRCa associated with the *V* allele comparing with *L* allele (Febbo *et al.*, 1999; Nam *et al.*, 2001), although other studies did not find such an association (Lamharzi *et al.*, 2003; Ntais *et al.*, 2003).

Despite the low frequency of the A49T *T* allele among healthy subjects in most populations, this allele is implicated in PRCa for several reasons: 1- an earlier study found almost 10% of PRCa cases had the *T* allele (Ross *et al.*, 1992); 2- the *T* allele was linked to progression and aggressiveness of PRCa in pathologic survey (Jaffe *et al.*, 1999); and 3- of all known mutations in the SRD5A2 gene, this substitution increased *in vitro* 5α-reductase enzymatic activity the most and increase level of circulating DHT in blood (Makridakis *et al.*, 1999; Allen *et al.*, 2003). This study, consistent with previous studies (Lamharzi *et al.*, 2003; Ntais *et al.*, 2003), found no statistically association risk between *T* allele and developing PRCa in BPH patients.

Although this study found no statistically significant associations of these SRD5A2 polymorphisms with

PRCa, a small effect of these markers cannot be ruled out because of the rarity of certain marker genotypes. Larger studies are required to further clarify the role of these markers and to elucidate whether genetic diversity of the *SRD5A2* gene, alone or in combination with other susceptibility genes, can help in detection BPH patients with a high risk of developing PRCa.

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### References

- Allen, N.E, Reichardt, J.K, Nguyen, H., and Key, T.J. 2003. Association between two polymorphisms in the *SRD5A2* gene and serum androgen concentrations in British men. *Cancer Epidemiol Biomarkers Prev.* 12: 578-581.
- Armenian, H.K, Lilienfeld, A.M, Diamond, E.L, and Bross, I.D. 1975. Epidemiologic characteristics of patients with prostatic neoplasms. *Am J Epidemiol.* 102: 47-54.
- Armenian, H.K, Lilienfeld, A.M, Diamond, E.L, and Bross, I.D. 1974. Relation between benign prostatic hyperplasia and cancer of the prostate. A prospective and retrospective study. *Lancet.* 2: 115-117.
- Bharaj, B., Scorilas, A., Giai, M., and Diamandis, E.P. 2000. TA repeat polymorphism of the 5 $\alpha$ -reductase gene and breast cancer. *Cancer Epidemiol Biomarkers Prev.* 9: 387-93.
- Bostwick, D.G, Cooner, W.H, Denis, L., Jones, G.W, Scardino, P.T, and Murphy, G.P. 1992. The association of benign prostatic hyperplasia and cancer of the prostate. *Cancer.* 70: 291-301.
- Carter, H.B, and Coffey, D.S. 1990. The prostate: an increasing medical problem. *Prostate.* 16: 39-48.
- Chen, T.T, and Heidelberger, C. 1969. In vitro malignant transformation of cells derived from mouse prostate in the presence of 3-methylcholanthrene. *J Natl Cancer Inst.* 42: 915-925.
- Davis, D.L and Russell, D.W. 1993. Unusual length polymorphism in human steroid 5  $\alpha$ -reductase type 2 gene (*SRD5A2*). *Hum Mol Genet.* 2: 820.
- Febbo, P.G, Kantoff, P.W, Platz, E.A, Casey, D., Batter, S., and Giovannucci, E. 1999. The V89L polymorphism in the 5- $\alpha$ -reductase type 2 gene and risk of prostate cancer. *Cancer Res.* 59: 5878-5881.
- Fraley, E.E, Ecker, S., and Vincent, M.M. 1970. Spontaneous in vitro neoplastic transformation of adult human prostatic epithelium. *Science.* 170: 540-542.
- Frank, T., Svoboda-Newman, S., and His, E. 1996. Comparison of methods for extracting DNA from formalin-fixed paraffin sections for nonisotopic PCR. *Diagn Mol Pathol.* 5:220-224.
- Franks, L.M, and Wilson, P.D. 1970. "Spontaneous" neoplastic transformation in vitro: the ultrastructure of the tissue culture cell. *Eur J Cancer.* 6: 517-523.
- Holund, B. 1980. Latent prostatic cancer in a consecutive autopsy series. *Scand J Urol Nephrol.* 14: 29-35.
- Hsieh, C., Thanos, A., Mitropoulos, D., Deliveliotis, Ch., Mantzoros, and C., Trichopoulos, D. 1999. Risk factors for prostate cancer: A case control study in Greece. *Int J Cancer.* 80: 699-703.
- Jaffe, J.M, Malkowicz, S.B, Walker, A.H, MacBride, S., Peschel, R., and Tomaszewski, J. 1999. Association of *SRD5A2* genotype and pathological characteristics of prostate tumors. *Cancer Res.* 59: 5878-5881.
- Kantoff, P., Febbo, P.G, Giovannucci, E., Krithivas, K., Dahl, D.M, Chang, G., Hennekens, C.H, Brown, M., and Stampfer, M.J. 1997. A polymorphism of the 5  $\alpha$ -reductase gene and its association with prostate cancer: a case-control analysis. *Cancer Epidemiol Biomarkers Prev.* 6: 189-192.
- Labrie, F., Sugimoto, Y., Luu-the V, Simard J., Lachance, Y., and Bachvarov, D. 1992. Structure of the human type II 5- $\alpha$ -reductase gene. *Endocrinology.* 131: 1571-1573.
- Lamharzi, N., Johnson, M.M, Goodman, G., Etzioni, R., Weiss, N.S, Dightman, D.A, Barnett, M, DiTommaso, D, and Chen, C. 2003. Polymorphic markers in the 5 $\alpha$ -reductase type II gene and the incidence of prostate cancer. *Int J Cancer.* 105: 480-483.
- Makridakis, N.M, Di Salle, E, and Reichardt, J.K. 2000. Biochemical and pharmacogenetic dissection of human steroid 5  $\alpha$ -reductase type II. *Pharmacogenetics.* 10: 407-413.
- Makridakis, N.M, Ross, R.K, Pike, M.C, Crocitto, L.E, Kolonel, L.N, Pearce, C.L, Henderson, B.E, and Reichardt, J.K. 1999. Association of mis-sense substitution in *SRD5A2* gene with prostate cancer in African-American and Hispanic men in Los Angeles, USA. *Lancet.* 18 :975-978.

- Mishina, T, Watanabe, H, Araki, H, and Nokao, M. 1985. Epidemiological study of prostatic cancer by matched pair analysis. *Prostate*. 6: 423-436.
- Nam, R.K, Toi, A, Vesprini, D, Ho, M, Chu, W, and Harvie, S. 2001. V89L polymorphism or type 2 5-alpha-reductase enzyme gene predicts prostate cancer presence and progression. *Urology*. 57: 199-204.
- Ntais, C, Polycarpou, A, and Ioannidis, J.P. 2003. SRD5A2 gene polymorphisms and the risk of prostate cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 12: 618-624.
- Parker, S.L, Tong, T, Bolden, S, and Wingo, P.A. 1996. Cancer statistics 1996. *CA Cancer J Clin*. 46: 5-27.
- Pienta, K, Goodson, J, and Esper, P. 1996. Epidemiology of prostate cancer: molecular and environmental clues. *Urology*. 48: 676-683.
- Prior, T, and Waxman J. 2000. Localised prostate cancer: can we do better? There have been some advances in local control, but little impact on survival. *BMJ*. 320: 69-70.
- Reichardt, J.K, Makridakis, N, Henderson, B.E, Yu, M.C, Pike, M.C, Ross, R.K. 1995. Genetic variability of the human SRD5A2 gene: implications for prostate cancer risk. *Cancer Res*. 55: 3973-3975.
- Ross, R.K, Bernstein, L, Lobo, R.A, Shimizu, H, Stanczyk, F.Z, Pike, M, and Henderson, B. 1992. 5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black males. *Lancet*. 339: 887-889.
- Schuman, L.M, Mandel, J., Blackard, C., Bauer, H., Scarlett, J., and McHugh, R. 1977. Epidemiologic study of prostatic cancer: preliminary report. *Cancer Treat Rep*. 61: 181-186.
- Schwartz, I, Wein, A.J, Malloy, T.R, and Glick, J.H. 1986. Prostatic cancer after prostatectomy for benign disease. *Cancer*. 58: 994-996.
- Tayeb, M.T, Clark, C, Sharp, L, Haites, N.E, Murray, G.I, and McLeod, H.L. 2003. CYP3A4 & VDR gene polymorphisms and the risk of prostate cancer in men with benign prostate hyperplasia. *British Journal of Cancer*. 928-932.
- Tayeb, M.T, Clark, C, Haites, N.E, Rooney, P.H, Murray, G.I, Payne, S.N.L, and McLeod, H.L. 2002. CYP3A4 promoter variant is associated with prostate cancer risk in men with benign prostate hypertrophy. *Oncology Reports*. 653-655.
- Tayeb, M.T., Clark, C, Haites, N.E., Rooney, P.H., Murray, G.I, Payne, S.N.L., and McLeod, H.L. 2004. Length and somatic mosaicism of CAG and GGN repeats in the androgen receptor gene and the risk of prostate cancer in men with benign prostate hyperplasia. *Annals of Saudi Medicine*. 21-26.
- Tayeb, M.T, Clark, C, Haites, N.E., Sharp, L, Murray, G.I, and McLeod, H.L. 2004. Vitamin D receptor, HER-2 polymorphisms and risk of prostate cancer in men with benign prostate hyperplasia. *Saudi Medical Journal*. 447-451.
- Thigpen, A.E, Davis, D.L, Milatovitch, A, Mendonca, B.B, Imperato-Ginley, J, and Griffin, J.F. 1992. Molecular genetics of steroid 5-alpha-reductase type 2 deficiency. *J Clin Invest*. 90: 799-809.
- Tzonou, A, Signorello, L.B, Lagiou, P, Wu, J, Trichopoulos, D, and Trichopoulou, A. 1999. Diet and cancer of the prostate: A case control study in Greece. *Int J Cancer*. 80: 704-708.
- Whittemore, A.S, Wu, A.H, Kolonel, L.N, John, E.M, Gallagher, R.P, Howe, G.R, and West, D.W. 1995. Family history and prostate cancer risk in black, white, and Asian men in the United State and Canada. *Am J Epidemiol*. 141: 732-740.
- Wingo, P.A, Bolden, S, Tong, T, Parker, S.L, Martin, L.M, and Heath, C.W. 1996. Cancer statistics for African Americans, 1996. *CA Cancer J Clin*. 46: 113-125.
- Zubiaga, A.M, Belasco, J.G, and Greenberg, M.E. 1995. The nonamer UUAUUUAUU is the key AU-rich sequence motif that mediates mRNA degradation. *Mol Cell Biol*. 15: 2219-2230.

الطفرات الجينية في مستقبلات الريدكتاز وعلاقتها بسرطان البروستات عند المصابين بورم البروستات الحميد

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**الملخص:** المقدمة والهدف: للتعرف على مدى إمكانية إستخدام الطفرات الجينية في مستقبلات الريدكتاز كتشخيص جيني مبكر لحدوث سرطان البروستات عند الرجال المصابين بورم البروستات الحميد. الطريقة: في هذه الدراسة جمعت العينات من مستشفى أبردين بأسكتلندا وهي عبارة عن أنسجة محفوظه في الشمع لمرضى أصيبو بورم البروستات الحميد وبعد فترة زمنية أصيبو بسرطان البروستات وعينات شمعية أخرى لمرضى أصيبو بورم البروستات الحميد ولم يصابو بسرطان البروستات. للتعرف على الطفرات الجينية استخدمنا PCR / ABI PRISM 310 RFLP / Sequencing. النتائج: قد تبين من هذه الدراسة أن الحاملين للطفرات الجينية لهذا الجين تكون نسبة أصابتهم بسرطان البروستات أعلى مقارنةً بالأشخاص الغير حاملين لهذه الطفرة الجينية الخاتمة: إن الكشف المبكر للطفرات الجينية لهذا الجين قد يساعد في التشخيص المبكر لسرطان البروستات عند الرجال المصابين سابقا بورم البروستات الحميد الأمر الذي سوف يمكننا من القيام بأجراء العلاج المبكر و المناسب لهم.. نتائج هذه الدراسة يجب أن تؤكد بدراسات أخرى عديدة للوقوف على أهمية هذه الطفرات في حدوث المرض.

**الكلمات مفتاحية:** الطفرات الجينية، مستقبل الريدكتاز، سرطان البروستات، ورم البروستات الحميد.