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Original Article

Association of TA Repeat Polymorphism of Steroid 5-Alpha-Reductase Type 2 Gene with Prostate Cancer in a Beninese Population

Association du Polymorphisme Répété TA du Gène de la Stéroïde 5-Alpha-Réductase de Type 2 Avec le Cancer de la Prostate dans une Population Béninoise

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ABSTRACT

Introduction. Genetic variants of 5-alpha-reductase type 2 (SRD5A2) have been associated with high-risk factors for prostate cancer (PCa). The purpose of this study was to determine the association between the SRD5A2 gene AT repeat polymorphism and total prostate-specific antigen (TPSA) level on one hand, and PCa grade on the other. **Materials and Methods**. This was a descriptive and analytical cross-sectional study conducted from January 2018 to September 2022 at the CNHU-HKM Urology-Andrology University Clinic. TPSA levels were determined by radioimmunoassay. PCa Gleason scores and ISUP 2016 classification were defined by pathological examination of biopsies. PCR was used to determine the different genotypes of the SRD5A2 gene AT repeat polymorphism. The association between genotypes and clinical data was studied using the proportion and Student's t-tests. **Results**. The inclusion criteria were met by 140 cancer patients. The average age was 59.62 years, with 9.16 years as a standard deviation. The TPSA levels averaged 104.87 ng/ml, with 160.96 ng/ml as a standard deviation. Histologically, 58.57% of cases had a Gleason score ≥ 8, with 50.71% classified as ISUP 4 and 7.86% as ISUP 5. In the study population, the genotypes SRD5A2-L/SRD5A2-L and SRD5A2-L/SRD5A2-S were respectively 58.57% and 41.43%. Statistical analyses revealed highly significant differences between SRD5A2 genotypes when considering respectively TPSA levels and the ISUP 2016 groups. **Conclusion.** Very high levels of TPSA and a high-risk of PCa were associated with the SRD5A2-L/SRD5A2-L genotype. It has the potential to be used as a genetic marker for screening and early diagnosis of PCa.

RÉSUMÉ

Introduction. Le gène de la 5-alpha-réductase de type 2 (SRD5A2) était reconnu comme un gène qui prédisposait au cancer de la prostate (CaP). Notre objectif était de déterminer l'association entre le polymorphisme AT répété de ce gène, le taux de l'antigène spécifique de la prostate total (PSA-T) et le grade du CaP. **Méthodes**. Il s'agissait d'une étude transversale descriptive et analytique menée de janvier 2018 à septembre 2022 à la clinique universitaire d'urologie-andrologie du CNHU-HKM. Les taux de PSA-T étaient déterminés par le dosage radio-immunologique. Les scores de Gleason du CaP et la classification ISUP 2016 étaient définis par l'examen anatomopathologique des biopsies. Les génotypes (AT)n du gène SRD5A2 étaient déterminés par la technique de PCR. L'association entre les données génétiques et cliniques était étudiée grâce au test de proportions et au test de Student. **Résultats**. 140 cas de CaP ont répondu aux critères d'inclusion. L'âge moyen était de 59,62 ans. Le taux moyen de PSA-T était de 104,87 ng/ml. 58,57 % des cas avaient un score de Gleason ≥ 8 avec 50,71% classé ISUP 4 et 7,86% classé ISUP 5. Les génotypes SRD5A2-L/SRD5A2-L et SRD5A2-L/SRD5A2-S représentaient respectivement 58,57 % et 41,43 %. Il y avait des différences hautement significatives entre les génotypes SRD5A2, les taux de PSA-T et les groupes ISUP 2016. **Conclusion**. Des niveaux très élevés de PSA-T et un risque élevé de CaP sont associés au génotype SRD5A2-L/SRD5A2-L. Il pourrait être utilisé comme un marqueur génétique de dépistage et de diagnostic précoce du CaP.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer, behind lung cancer, and the sixth most common cause of cancer death in men worldwide. In developed countries, it is more prevalent, but rates have also increased in underdeveloped countries in recent years. It has an incidence of between 19.5 and 22 cases per 100,000 inhabitants on the African continent. Several epidemiological studies conducted worldwide have shown that PCa incidence and mortality rates are generally higher in predominantly black African populations than in other races [1]. Some of these variations have been attributed to a combination of epidemiological, genetic, or environmental causes. Today, the only obvious risk factors are age, ethnicity, and family history. It is believed that a series of specific genetic abnormalities, both acquired and inherited, is the cause of prostatic carcinogenesis. The diversity of gene allele expression confirms the hypothesis of a mutagenic etiology that differs from one population to another. The distribution of alleles of these genes may differ significantly according to ethnic group. In PCa, the presence of alleles of certain genes involved in androgen metabolism (SRD5A2, or varying receptivity to steroid hormones (androgen receptor, vitamin D receptor)) may be partly responsible for the variations in incidence noted between populations studied at the epidemiological level [2]. The conversion of testosterone to active dihydrotestosterone (DHT) is believed to be done by the SRD5A2 isoform. Genetic variants of this enzyme are associated with an increased risk of PCa [2, 3]. In Benin, no genetic studies have been conducted on PCa. Usually, PCa is detected in its advanced stage and has a high rate of specific mortality [4]. Analyzing the SRD5A2 gene polymorphism and its potential role in the onset of PCa would be useful for screening and early diagnosis strategies. This study aimed to determine the association between the SRD5A2 gene AT repeat ((AT) n) polymorphism, TPSA levels, and PCa grades.

MATERIALS AND METHODS

Sampling

This descriptive and analytical cross-sectional study was conducted from January 8, 2018, to September 25, 2022, at the Laboratory of Molecular Genetics and Genome Analysis of the Faculty of Science and Technology of the University of Abomey-Calavi (LGMAG/FAST/UAC). All participants in this study have signed an informed consent form, as recommended by the National Ethics Committee for Health Research (CNERS) (under the authorization number IRB00006860, dated 31/10/2017). To ensure animal welfare and protect animal rights, no animal experiments were carried out in this study.

140 cancer patients aged between 50 and 80 years were recruited at Hubert K. MAGA National University Hospital's University Clinic of Urology-Andrology based on the following criteria: rectal examination (RE) suspicious on clinical examination; PSA level greater than 4 ng/ml; no history of adenoma or prostate cancer; PCa diagnosis of confirmed by anatomo-pathological examination; a Beninese residing in Benin for at least 5 years, no other known cancer or lytic bone disease..

Radioimmunoassays for TPSA

Radioimmunoassays for TPSA were performed at the Radioimmunoassay Service of the Faculty of Health Sciences at the University of Abomey-Calavi using the IRMA KIT-BECKMAN total PSA. A dry tube was used to collect 5 ml of blood from each patient. All assays were performed using 100 µL blood serum. The level of TPSA was measured in nanograms per milliliter (ng/ml).

Prostate biopsies and anatomopathological examinations

Prostate biopsies were taken at the CUUA/CNHU-HKM and fixed in 10% formalin. Anatomopathological examinations of the biopsies were carried out at the Anatomical Pathology and Cytology Laboratory, Faculty of Health Sciences.

Total genomic DNA extraction from blood

Total genomic DNA was extracted from blood samples collected in EDTA tubes according to the protocol described by Sègbo et al. [5]. 2 µL of each genomic DNA extract were visualized on a 1% agarose gel, and the remaining extracts were stored at -20°C.

Genotyping

The identification of different genotypes was based on the analysis of total genomic DNA using the classic polymerase chain reaction (PCR) technique, which amplifies microsatellites with marker-specific primer pairs, as described by Davis et al. [2], who observed that the size of SRD5A2 gene amplifiates varied from 170bp to 195bp in humans.

Genetic amplification of the poly-TA microsatellite of the SRD5A2 gene was performed following the method described by Véronique-Baudin et al. [6], with a few modifications. The reaction volume was 20µl and contained 5x PCR buffer (green buffer), 10 mM dNTP, 10 µM of each primer, 5 U /µl Taq polymerase, 3µl of approx. 20ng/ µl genomic DNA. The amplification program was as follows: an initial 4 min pre-denaturation step at 95°C, followed by 35 cycles, each including 30 s of denaturation at 95°C, primer hybridization at 51°C for 1 min, and 1 min elongation at 72°C. The final extension step was performed at 72°C for 5 min.

PCR products (5 µl) were detected on a 2.5% agarose gel that contained 1.5 µl of Ethidium Bromide (EB). The migration process was carried out using 0.5X TBE (Tris Boric Acid EDTA) buffer at 100V for 45 minutes. To visualize the electrophoretic bands, we used a Trans UVP illuminator. Amplify sizes were estimated by comparing them with an associated size marker and literature data.

Statistical analysis

To study the association of different SRD5A2 genotypes with TPSA levels as well as PCa grades, the TPSA levels were divided into two groups: $5 < TPSA \leq 20$ ng/ml and $TPSA > 20$ ng/ml. Similarly, the PCa grades were divided into five groups according to the ISUP 2016 classification. For each genotype of the SRD5A2 gene, the frequencies of the two TPSA groups and the five ISUP groups were calculated, and the frequency tables were analyzed using proportional tests. Student’s t-test was used to compare

SRD5A2 genotypes based on TPSA levels, while analysis of variance (ANOVA) was used to compare PCa ISUP groups based on TPSA levels. All analyses were conducted using the R software.

RESULTS

Age distribution of patients

All cancer patients' ages were recorded and ranged from 50 to 80 years, with a mean of 59.62 years and a standard deviation of 9.16 years. Table 1 shows the age distribution of the study population.

Table 1. Age distribution of patients

Age ranges (years)	N	%
[50-60[	69	49.29
[60-70[	45	32.14
[70-80]	26	18.57
Total	140	100

Clinical data

TPSA levels ranged from 5 to 1086.4 ng/ml. The mean TPSA level before any treatment was 104.87 ng/ml with a standard deviation of 160.96 ng/ml. Patients were classified according to the International Society of Urological Pathology (ISUP) 2016 groups during pathological anatomy examination. Figure 1 and 2 show the distribution of patients according to according to TPSA levels and ISUP groups, respectively.

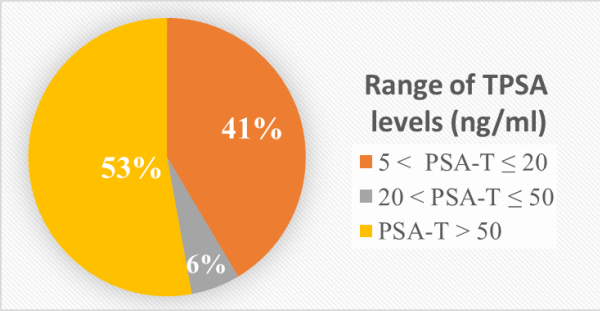

Figure 1. The distribution of patients according to TPSA levels

Abbreviations: %, percentage; TPSA, total prostate-specific antigen; ng, nanograms; ml, milliliter.

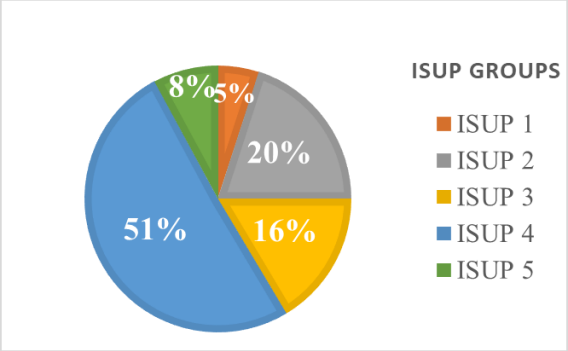

Figure 2. The distribution of patients according to the ISUP groups

Abbreviations: ISUP, International Society of Urological Pathology

SRD5A2 gene (AT)n polymorphisms

Figure 3 shows the results of electrophoretic migration of PCR products.

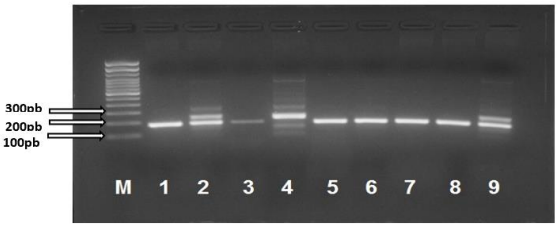

Figure 3. Electrophoregram showing SRD5A2 genotypes

Abbreviations: M, 100bp markers; 1, 2, 3, 4, 5, 6, 7, 8 and 9, PCR products.

On the electrophoregram, the 170 bp band represents the short allele (S) and the other bands (195bp, 200bp, 200-300bp, and 300bp) represent the long alleles (L). Wells 1, 3, 5, 6, 7, and 8 correspond to the SRD5A2-L/SRD5A2-L genotype, and wells 2, 4, and 9 correspond to the SRD5A2-L/SRD5A2-S genotype. Table 2 shows the frequencies of the different SRD5A2 genotypes in the study population.

Table 2. Frequencies of different SRD5A2 genotypes

SRD5A2 genotypes	N	%
SRD5A2-L/SRD5A2-L	82	58,57
RD5A2-L/SRD5A2-S	58	41,43
SRD5A2-S/SRD5A2-S	00	00,00
Total	140	100

Abbreviations: L, long allele; S, short allele; SRD5A2, 5-alpha-reductase type 2.

Statistical results

The results of the SRD5A2 genotype proportion test according to TPSA levels are shown in Table 3. Patients with the SRD5A2-L/SRD5A2-S genotype had TPSA levels between 5 and 20 ng/mL, whereas those with the SRD5A2-L/SRD5A2-L genotype had TPSA levels above 20 ng/mL. The proportions test showed a highly significant difference between the proportions of patients considered for SRD5A2 genotypes according to TPSA levels (p-value < 0.0001).

Table 3. Results of the SRD5A2 genotype proportion test according to TPSA levels

SRD5A2 genotypes	5 < TPSA ≤ 20 (ng/ml)	TPSA >20 (ng/ml)	p-value
	N		
SRD5A2-L/SRD5A2-S	58	0	< 0.0001
SRD5A2-L/SRD5A2-L	0	82	< 0.0001

Abbreviations: TPSA = total prostate-specific antigen; ng = nanograms; ml = milliliter; L = long allele; S = short allele; SRD5A2 = 5-alpha-reductase type 2.

Table 4 shows the results of the proportion test of SRD5A2 genotypes according to ISUP 2016 groups. PCas were classified as ISUP 1, ISUP 2, and ISUP 3, with a dominance of the ISUP 2 group (28 patients), and were observed in SRD5A2-L/SRD5A2-S heterozygous patients. Homozygous SRD5A2-L/SRD5A2-L patients were in the ISUP 4 and ISUP 5 groups, with ISUP 4 dominating (71 patients). The proportion test showed a

highly significant difference between the SRD5A2 genotypes and the ISUP 2016 groups (p-value < 0.0001).

Table 4. Results of the SRD5A2 gene proportion test according to ISUP 2016 groups

SRD5A2 genotypes	ISUP1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	p-value
			N			
SRD5A2-L/SRD5A2-S	7	28	23	0	0	< 0.0001
SRD5A2-L/SRD5A2-L	0	0	0	71	11	< 0.0001

Abbreviations: L = long allele; S = short allele; ISUP = International Society of Urological Pathology; SRD5A2 = 5-alpha-reductase type 2

DISCUSSION

At the time of PCa diagnosis, the mean age of patients was 59.62 years (with extremes of 50 and 80 years) and a standard deviation of 9.16 years. This is because, by the 2022 age pyramid, the 15 to 64 age group represents 52.18% (men 3.595.897/women 3.823.786) of the Beninese population [7]. Our results are similar to those of Rebbeck and Jeanteur, who considered that in sub-Saharan Africa, PCa develops mainly in relatively young subjects (average age under 60) [8, 9]. The average age of our patients is close to that of Seidou et al., Ludovic et al., Mahamat et al., Ikuerowo et al., Niang et al. and Ravery et al. who found respectively 65.7, 57, 61.2, 64.2, 65 and 61.4 years of age at diagnosis [10,11, 12, 13, 14,15].

The average TPSA level was found to be 104.87 ng/ml and had a standard deviation of 160.96 ng/ml. In 52.86% of the cases, the TPSA value was higher than 50 ng/ml, indicating early metastatic expansion. A relationship exists between TPSA levels and early metastatic expansion of PCa. In cases where TPSA values exceed 50 ng/ml, extraprostatic participation occurs in 80% of cases [16]. Yevi et al. observed a high TPSA value at diagnosis in the same department in previous years [17]. The same observation has been made in other African series [18,19, 20, 21].This confirms the delay in diagnosing PCa in Black Africa, which is linked to the natural history of the disease, the lack of public information and awareness policy, men's concerns about coming to urology consultations, and problems of access to health services. Our genetic study revealed that 82 patients had the SRD5A2-L/SRD5A2-L genotype with a TPSA level above 20 ng/ml, and 58 patients had the SRD5A2-L/SRD5A2-S genotype with a TPSA level between 5 and 20 ng/ml. Our findings indicated that the L/L and L/S genotypes of the SRD5A2 gene were highly significantly associated with TPSA levels ($p < 0.0001$). The long allele (TA)9 of the SRD5A2 gene was associated with high TPSA levels. Our results is comparable to the work of Rajender et al. who showed that in the SRD5A2 gene, the presence of the long allele (TA)9 of the polymorphic site (TA)n with the Val/Leu and Leu/Leu genotypes of the V89L polymorphic site was correlated with higher levels of TPSA compared with the Val/Val genotype of the V89L polymorphic site [22].

For the histoprognostic grade, 58.57% of PCa patients had a Gleason score ≥ 8, with 71(50.71% of cases) classified as ISUP 4 and 11(7.86% of cases) as ISUP 5. These results reflect high-risk PCa, which can be explained by delayed diagnosis. Our results are comparable with those of Yevi et al., who also reported a high rate of ISUP4 patients [17]. Several authors have made the same observation in African findings [23, 24, 25, 14, 26, 27]. Genetically, most patients (58.57% of cases) had the SRD5A2-L/SRD5A2-L genotype, with 50.71% classified as ISUP 4 and 7.86% as ISUP 5. In terms of the SRD5A2-L/SRD5A2-S genotype, 41.43% of patients were enrolled, including 20.00% classified as ISUP 2, 16.43% as ISUP 3, and 5.00% as ISUP 1. L/L and L/S genotypes of the SRD5A2 gene were highly significantly associated with ISUP 2016 groups in our study ($p < 0.0001$). Thus, the homozygous SRD5A2-L/SRD5A2-L genotype was associated with high-risk PCa. Our results fit with observations in the literature, which have estimated that the long allele (TA)18 of the SRD5A2 gene is more frequently found in populations of African origin, which have a very high incidence of CaP [2, 3, 28]. Type 2 5-alpha-reductase enzyme converts testosterone into dihydrotestosterone (DHT) which binds to the androgen receptor. DHT metabolite levels are higher in melanodermic subjects and Caucasians than in Asians [29]. Polymorphism of the SRD5A2 gene, encoding the synthesis of the 5-alpha-reductase type 2 enzyme, could modify the regulation of this gene's expression [30], and thus DHT levels, conferring increased susceptibility to CaP in people with the (TA) 9 and (TA)18 alleles or with the A49T mutation. It is important to note that our sample did not include the SRD5A2-S/SRD5A2-S genotype, but this does not necessarily mean that this genotype does not exist in Benin. Further studies are needed to determine its presence. In a previous study by Davis et al [2] they found that the size of SRD5A2 gene amplifiates in the human species ranged from 170pb to 195pb. However, we observed amplifiats of various sizes in our study including 170pb, 195pb, 200pb, 200 - 300pb and 300pb. The new amplifiats (200pb, 200 - 300pb and 300pb) are non-specific and would be obtained because of the experimental conditions.

Our study's findings will help in the early detection and diagnosis of prostate cancer (PCa) in Benin, which could ultimately lead to a decrease in the incidence of this disease.

CONCLUSION

Our study population showed the SRD5A2 gene (AT)n polymorphism. The SRD5A2-L/SRD5A2-L genotype is associated with high TPSA levels and a higher risk of PCa. This genotype will be used as a genetic marker for screening and early diagnosis of prostate cancer. To assess the predictive value of this genetic marker, we will conduct case-control studies of SRD5A2 gene (AT)n polymorphisms in the Beninese population.

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AUTHOR CONTRIBUTIONS

The following are the tasks realized by the team members for the study: Conceptualization: A.B.J. and S.A.G.J.; Data generation: A.B.J., S.A.G.J., Y.D.I.M., M.A.A., A.M.M., S.P., H.G.D., A.D.G.J., L.F., G.F., A.M-T., A-G.K.M., and A.C.; Data acquisition: A.B.J. and S.A.G.J.; Data assessment and interpretation: A.B.J., S.A.G.J., and Y.D.I.M.; Statistical analysis: A.B.J. and S.A.G.J.; Funding obtaining: A.B.J. and S.A.G.J.; Original manuscript writing: A.B.J. and S.A.G.J.; All authors contributed to and approved the final manuscript.

CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

ETHICAL APPROVAL AND CONSENT TO TAKE PART

This study was approved by the National Ethics Committee for Health Research (NECHR) on 31/10/2017 under the code IRB00006860. All participants provided informed consent, and no animal experiments were conducted to ensure animal welfare.

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HIGHLIGHTS OF THE STUDY

What is known on this topic

In prostatic cancer (PCa), the presence of alleles of certain genes involved in androgen metabolism (SRD5A2, or varying receptivity to steroid hormones (androgen receptor, vitamin D receptor)) may be partly responsible for the variations in incidence noted between populations. Genetic variants of this enzyme are associated with an increased risk of PCa [2, 3]. In Benin, no genetic studies have been conducted on PCa In Benin, no study on the association of genetic variants of SRD5A2 gene with PCa. have been conducted.

The question this study addresses

Association between TA repeat polymorphism of SRD5A2 gene and PCa in a Beninese population

What this study adds to our knowledge

The SRD5A2 gene (AT) n polymorphism exists in Beninese population. The SRD5A2-L/SRD5A2-L genotype is associated with high TPSA levels and a higher risk of PCa.

How this is relevant to practice, policy or further research

The SRD5A2-L/SRD5A2-L genotype will be used as a genetic marker for screening and early diagnosis of prostate cancer.