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전립선특이항원 촉진염기서열 부위에서의 유전자 다형성과 전립선비대증 표현형의 관련성에 관한 연구

조선대학교 대학원

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The association between polymorphisms in prostate-specific antigen gene promoter and the phenotypes of benign prostate hyperplasia

2010년 8월 25일

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이 논문을 의학박사학위신청 논문으로 제출함

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초 록

전립선특이항원 촉진염기서열 부위에서의 유전자 다형성과 전립선비대증 표현형의 관련성에 관한 연구

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목적 : 전립선특이항원 (Prostate-specific antigen: PSA) 유전자의 유전적 다양성은 혈청 PSA 치와 관련되어있다. 5알파-환원효소 억제제(5α-reductase inhibitors: 5ARI)를 투여받는 환자들에서 나타나는 혈청 PSA의 폭넓은 변화는 유전적 수준에서의 개체 내 차이에 기인한 것일 수 있다. 본 저자들은 한국인 전립선비대증 환자들에서 PSA 촉진염기서열 부위의 유전적 다양성과 5알파-환원효소 억제제인 dutasteride 투여후 혈청 PSA의 변화 사이의 연관성에 대해 연구하였다.

대상 및 방법 : 전체 121명의 전립선비대증 환자들을 대상으로 dutasteride 투여 전과 투여 후 3개월째 혈청 PSA치를 측정하였다. 저자들은 PSA 유전자의 촉진염기서열부위 (transcription의 시작부위로부터 nucleotide 위치 -158에서 -356, 그리고 -5217에서 -5429까지)를 증폭시켰고, 그리고 증폭 산물을 자동염기서열 장치를 이용하여 유전자 다향성을 조사하였다.

결과 : 비교적 특성이 잘 파악된 세 개의 단일염기변형 (Single nucleotide polymorphism: SNP) (rs3760722, rs266867, rs266868), 특성이 파악되지 않은 여섯 개의 SNPs (rs17554958, rs266882, rs4802754, rs2739448, rs2569733, rs17526278), 그리고 한 개의 새로운 SNP (nucleotide 위치 -5402)가 발견되었다. PSA 촉진염기서열 부위의 어떠한 SNP도 연령보정 전립선 크기, 초기 PSA치, dutasteride 투여 3개월 후의 PSA 변화 등과 통계적으로 유의한 상관관계를 보이지 않았다. 그러나 -5217, -5307, 그리고 -5412 위치에서 한가지 하플로타입은 초기 PSA 치와 통계적 연관성을 보였다.

결론 : 기존에 알려진 것과 다르게 PSA 촉진염기서열 부위의 각각의 SNP는 전립선비대증 표현형과 관련성을 보이지 않는다. 저자들은 한국인 전립선비대증 환자에서 PSA 촉진염기서열부위 유전자형을 가지고 dutasteride 투여 후 혈청 PSA 변화를 예측할 수 없었다. 그러나 하플로타입 분석에서 초기 PSA치와 통계적 연관성을 보인 점은 유전적 관련성에 대한 단서로 추정된다.

Key Words: Benign prostate hyperplasia, Single nucleotide polymorphism, PSA promoter, PSA variation

Introduction

The incidence of benign prostate hyperplasia (BPH) is about 70% at 70 years of age, and has become nearly universal with advancing age [1]. Even though several hypotheses as to the trigger for BPH have been suggested, its main cause appears to be augmented levels of the androgen or dihydrotestosterone (DHT) [2]. Thus, intervention to reduce DHT in hypertrophied prostates has been a primary treatment target for BPH [3].

Two 5α-reductase inhibitors (5ARIs), finasteride and dutasteride, are currently available for reducing intra-prostatic DHT levels [2,3]. 5ARIs shrink prostatic epithelial cells and reduce their exocrine secretion, resulting the reduction of intraprostatic and serum prostate-specific antigen (PSA) levels [2-4].

Because the prostate is the major site of PSA expression in men, serum PSA levels have become the most widely used marker for both prostate cancer (PC) screening and for monitoring patients' responses to therapeutic interventions [5,6]. However, its use as a diagnostic marker is controversial because it has several limitations, including low specificity and low sensitivity for PC detection [7]. Furthermore, PSA levels have been shown to be highly variable over time. In addition, the serum PSA levels after 5ARIs treatments have revealed a considerable degree of variability [3,8]. As such, the inconsistent effects of 5ARIs on serum PSA levels have a limited ability to differentiate BPH from PC. To overcome these limitations, over the last decade there has been considerable research performed investigating PSA kinetics after 5ARIs application [9].

Recently, Crammer et al. reported that genetic variations in the PSA promoter are associated with serum PSA levels in men [10]. This finding implies that PSA promoter genotype information may help to understand the PSA kinetics after dutasteride treatment and, possibly, be used to refine models of PSA cutoff values to increase the sensitivity or specificity in detecting PC. However, whether these findings are universal for all people or just specifically for a European-origin population is not clear. Moreover, it is

known that reference ranges of PSA differ significantly according to race [11,12]. An additional problem is that because the population enrolled in this study was comprised of workers for a study of the interaction of asbestos exposure with genetic and environmental factors, neither the serum PSA levels nor genetic phenotypes were representative of clinical BPH patients [10]. Because of a significant overlap in PSA values between patients with BPH and PC, and a frequent coexistence of BPH and PC in aging men, a genetic study of BPH patients—not just men from the general population—must be performed to gain a further understanding of PSA pharmacokinetics and its differentiation from PC.

Thus, our aim is to evaluate the genetic variations in PSA promoters of Korean BPH patients, and then to compare the results with the BPH phenotypes and serum PSA changes after dutasteride treatment. We also focus on the genetic differences in PSA promoters among different ethnicities, which can reflect different phenotypes in prostate diseases.

Materials and Methods.

1. Study population

The study population is comprised of 121 Korean men having a clinical diagnosis of BPH (Table 1). Informed consent was obtained from all the study participants. The research protocol was approved by the Institutional Review Board at the Dankook University Hospital.

To exclude PC, transrectal core biopsies were performed on patients having serum PSA levels of > 4 ng/mL. From each patient, blood samples were collected in tubes containing sodium EDTA [13]. We used a QIAmp blood extraction kit (Qiagen, Valencia, CA, USA) for DNA extraction. Serum PSA levels were then evaluated using a PSA kit (PSA-RIACT, CIS Bio International, France) and prostate size was evaluated through a transrectal ultrasound (HD7 ultrasound system, Philips). We prescribed one tablet of dutasteride (0.5 mg/day, GSK, Beinheim, France) for 3 months and

sampled the blood to evaluate serum PSA changes. The changes were calculated as ratio (PSA level at 3 months / initial PSA level). Note that three people were lost at the 3-month period of this study.

2. Laboratory assay

DNA samples from the 121 patients were amplified via polymerase chain reaction (PCR). All PCR products yielded the required amplifications, but approximately 6% of the samples failed to yield specific genetic information or partially ambiguous DNA sequencing data. The ambiguous sequencing data at specific single nucleotide polymorphism (SNP) sites were excluded from the data analysis.

We performed PCR to amplify two regions in the PSA promoter area, one region around -158 to -356 and the other region around -5217 to -5429 from the transcription site (Fig. 1). The primer sequences of the -158 to -356 region were 5´-GGGATCAGGGAGTCTCACAA-3´ and 5´-AAACCTTCATTCCCCAGGAC-3´, respectively. And the primer sequences of the -5217 to -5429 region were 5´-TGTTAGCCAGGATGGTCTCA-3´ and 5´-CCTCAGAGCCTGAGAGGTCA-3´, respectively. PCR was performed in a 2720 Thermal Cycler (Applied Biosystems, Foster City, CA, USA). We used 25–70 ng of genomic DNA as the template, for a total PCR volume of 50 μL. Each tube contained 25 μL of 2× GoTaq Green Master Mix [400μM dATP, 400μM dGTP, 400μM dCTP, 400μM dTTP and 3 mM $MgCl_2$](Promega, Madison, WI, USA), 300 nM of each oligonucleotide primer, and 2 μL of the extracted DNA template. All reaction samples were heated to 94 °C for 5 min and then subjected to 30 cycles of 95 °C for 1 min, 55 °C for 1 min, and 72 °C for 1 min, with a final extension performed at 72 °C for 5 min. After purification (Bioneer, Daejeon, Korea), we identified the sequences using a BigDye Terminator Sequencing Kit (Applied Biosystems) using the above four primers (Fig. 1).

3. Statistical methods

Hardy-Weinberg equilibrium tests for all genotyped SNPs, and pairwise linkage disequilibrium tests for all pairs of genotyped SNPs were performed using the Haploview software package [14]. Lewontin's D´ was then used to estimate the strength of the pairwise linkage disequilibrium. And associations between the genetic variations and BPH phenotypes were estimated using SPSS software for Windows (version 11; SPSS, Chicago, IL, USA). *P* values < 0.05 were considered as being statistically significant.

Results

We identified 10 SNPs in this region (Fig. 2). Three relatively well characterized SNPs (rs3760722, rs266867, rs266868), six uncharacterized SNPs (rs17554958, rs266882, rs4802754, rs2739448, rs2569733, rs17526278,), and one novel SNP (nucleotide position -5412) were found. One polymorphism at -206 (rs17554958) was a T insertion or deletion variation (Fig. 3), and the other nine polymorphisms displayed a typical SNP phenotype, two homo-, and one hetero-genotypes. Because rs3760722 significantly deviated from the Hardy-Weinberg equilibrium (HWE) (*P*=0.002), it was removed from further statistical analysis.

The 121 study subjects from whom those samples were obtained had a mean (± standard deviation) age of 70.33 (±6.92) years, and a serum PSA concentration of 6.56 (±8.48) ng/mL. There were no statistical significances in the age intervals among the genetic variations for each SNP and no SNPs were statistically significantly associated with the initial serum PSA level, prostate volume, or PSA changes after 3 months of dutasteride treatment (Table 2). We performed a haplotype analysis for eight SNPs via the associated Haploview software. Our results showed one typical haplotype at -5217, -5307, and -5412. Haplotype 1 (TGC), haplotype 2 (TAT), haplotype 3 (AGT), and haplotype 4 (TGT) were estimated a frequency of 41.7%, 31.5%, 15.2%, and 10.6%, respectively.

We then tested whether specific combinations of these sequence variants

were associated with BPH phenotypes. As shown in Table 3, our study population had two major haplotypes. Men who had one copy of the -5217 TT/-5307AA or AG/-5412CC haplotype had statistically significantly higher PSA levels than men who had copies of the -5217AA or AT/-5307 GG/-5412 TT or CT (P=0.012, adjusted for age). However, other phenotypes such as prostate size and PSA changes after dutasteride treatment were not found to be associated with the above haplotype. In addition, pairwise linkage disequilibrium tests demonstrated that some of the SNPs examined in the PSA gene promoter were in strong linkage disequilibrium, but others were not (Table 4).

Discussion

Testosterone is converted to more potent DHT via a steroid 5α-reductase enzyme that binds to and activates androgen receptors [2]. The activated androgen receptor subsequently mediates and up-regulates the expression of PSA through androgen response elements (AREs) in the promoter area. Interventions that inhibit 5α-reductase enzymes inactivate androgen receptors and finally down-regulates serum PSA levels [2,15]. Thus, the median change in PSA in previous dutasteride treated patients was -59.5% at 2 years, which increased to -66.1% at 4 years [3]. Even though our study evaluated early changes in serum PSA after dutasteride treatment, it similarly reduced the serum PSA levels into 25% of initial PSA levels.

Even though the serum PSA levels after 5ARIs application was generally reduced, there are inter-personal variations in the reduced PSA levels. Since PSA variation makes it increasingly difficult to differentiate BPH patients from PC, furthering the comprehensive understanding of PSA pharmacokinetics and the scientific prediction of personal PSA changes after 5ARIs has a great practical significance [3,10,16].

There have been a number of recent studies investigating individual PSA variations according to genetic polymorphism in the PSA promoter area. For example, Xue et al. [17] reported serum PSA is associated with the PSA

genotype at -158, with PSA levels higher among men with the PSA AA genotype compared to men with the AG or GG genotypes. This polymorphism has also been associated with an increased risk for the development of PC [18,19], though another group has refuted this claim, reporting that this polymorphism was not associated with serum PSA levels in two separate groups of men without PC [20,21].

However, in a more recent study, the PSA promoter genes near -6 kb in the 5´ region (-4643G/A SNP (G allele), -5412C/T SNP (C allele), and -5429T/G SNP (G allele)) were associated with increased serum PSA levels. They concluded that genetic variations in the PSA promoter area are associated with serum PSA levels in men with no prostatic disease. From the above point of view, it was explained that PSA promoter genotype information may help refine models of PSA cutoff values [10,18,19].

Each individual has a change in DNA sequence of approximately 1 DNA base in every 200─300 bases compared to other individuals [22]. The ARE areas in our study showed 10 SNPs for about 800 bases; this high incidence of SNP in the ARE area may be responsible for different phenotypes or inherited individual differences in BPH or PC phenotypes.

Three polymorphism sites such as rs3760722, rs266867, and rs266868 were well characterized in HapMap information. The genotypes of rs266868 in Japanese and Chinese from HapMap data were that GG type 36% and 47%, AG type 45% and 46%, and AA type 18% and 6%, respectively. Our results for Korean patients revealed similar data; GG type 47.3%, AG type 40.3%, and AA type 12.2%. The genotypes of rs266867 in Japanese and Chinese were that AA type 1.2% and 3.6%, AT type 29.4% and 38.1%, and TT type 69.4% and 58.3%, respectively; our data was AA type 2.6%, AT type 27.1%, and TT type 70.1%.

Six uncharacterized SNPs (rs17554958, rs266882, rs4802754, rs2739448, rs2569733, rs17526278) were found. The polymorphism at -206 (rs17554958) was a T insertion or deletion variation, whereas the other five polymorphisms showed two homo-, and one hetero-genotype variations. One

novel SNP (nucleotide position -5402) was also found. However, because the incidence of CT and TT genotypes were rare, 1.6% and 0.8% in the novel SNP, large numbers of samples are needed for their characterization.

The 121 patients in this study had a mean (± standard deviation) age of 70.33 (±6.92) years, and a serum PSA concentration of 6.56 (±8.48) ng/mL. Because the serum PSA from this population was higher than in other studies, it was thought that some patients in our study may have PC. To reduce possible contamination with PC, we routinely took a prostate biopsy from the patients having a serum PSA > 4 ng/mL. In total, 16 patients with > 10 ng/mL serum PSA were given prostate biopsies, with subsequent follow up for at least 2 years after dutasteride treatment. Over this period, they all showed continuously decreasing serum PSA levels suggesting BPH.

It is well known that patients with and without PC show a consistent decrease in median PSA from baseline within an early period after initial dutasteride treatment. However, from month 12 and thereafter there was an increase in median PSA in patients eventually diagnosed with PC, whereas in those without a subsequent diagnosis of PC median PSA levels continued to decrease [3,16].

There were no statistical significances in age intervals among the genetic variations in each SNP. Interestingly, all SNPs were not statistically significantly associated with the serum PSA level, prostate volume, or PSA changes after 3 months of dutasteride treatment (Table 2); our results were different from the report by Cramer et al. [10].

There could be several reasons for these differences. First, the characteristics of the patients enrolled in this study were different. Cramer et al. included asbestos workers who were recruited for a study of the interaction of asbestos exposure with genetic and environmental factors [10]. Moreover, their patients were younger, and had a median serum PSA concentration that was lower than in our patients. Our population was comprised of clinical BPH patients who complained of lower urinary tract symptoms (LUTS). Furthermore, all patients who underwent ultrasound

showed a large prostate volume (> 30 cc); there is a clinically significant relationship between serum PSA and prostate volume in men with BPH [6,8]. Most of our population had a large size prostate volume, which indicated that dutasteride treatment was required.

We must also consider the ethnical differences between Caucasians and Asians. Oesterling et al. [12] reported that age specific reference ranges were lower for serum PSA levels and higher for PSA densities in Japanese men, relative to Caucasian men. As PSA levels depend markedly on age and might be significantly influenced by race, a given PSA value may have a markedly different clinical meaning for patients of different races [11,12].

Using Haploview software, we performed halpotype analyses of nine SNPs. Pairwise linkage disequilibrium tests demonstrated that most of the SNPs examined in the upper area of the PSA gene promoter (-5307 to -5429) were in a strong linkage disequilibrium (Table 4). However, there was weak linkage disequilibrium between the -158 SNP and the upper area of the PSA gene. Again, this result was different from the study by Cramer et al. which included a linkage disequilibrium between the -158 SNP and SNPs further upstream. Thus, successive studies will be needed to define whether these differences originated from ethnical variations or different disease phenotypes [10].

The results showed one haplotype at -5217, -5307, and -5412. Haplotype 1 (TGC), haplotype 2 (TAT), haplotype 3 (AGT), and haplotype 4 (TGT) were then estimated a frequency of 41.7%, 31.5%, 15.2%, and 10.6%, respectively. Interestingly, men who had one copy of the -5217 TT/-5307AA or AG/-5412CC haplotype had statistically significantly higher PSA levels than men who had one copy of the -5217AA or AT/-5307 GG/-5412 TT or CT (P=0.012, adjusted for age). It should be noted at this time that we were not sure if this result has a clinical meaning or if it is a statistical error; further study is needed.

In summary, the present findings suggest that genetic variations in the PSA promoter area are not associated with initial PSA levels, prostate

volume, or PSA changes after dutasteride treatment in Korean BPH patients. Again, it was found that we cannot predict the serum PSA changes after dutasteride treatment with PSA promoter genotype alone in Korean BPH patients. However, the finding that one haplotype in -5217, -5307, and -5412 was associated with initial serum PSA level suggests a clue towards defining the genetic involvement. Additional research or a larger enrolled population is still required in order to determine the mechanisms of different patterns of the same PSA promoter gene among different racial groups.

Table 1. Clinical and demographic characteristics of study subjects

Sample size		*n*=121
Age, years		70.33 ± 6.92
Prostate size, cc		59.2 ± 28.76
<30	12	
30–<50	37	
≥50	56	
Not taken	16	
Initial serum PSA, ng/mL		6.56 ± 8.48
<4	58	
4–<10	47	
≥10	16	
Not taken	0	
PSA changes, %		0.75 ± 0.47
<0.5	34	
0.5–<1	65	
≥1	19	
Not taken	3	

PSA ; prostate-specific antigen

Table 2. Serum PSA levels, prostate volume and SNPs in PSA promoter region

SNP/genotype	N	Prostate volume (cc)	N	Initial PSA levels (ng/mL)	N	PSA changes
rs266882						
CC	65	59.51 ± 29.18	76	5.84 ± 5.83	75	0.71 ± 0.47
CT	34	57.01 ± 23.8	37	7.78 ± 12.44	36	0.68 ± 0.5
TT	0		1		1	
rs17554958						
Deletion	43	57.8 ± 28.06	49	6.73 ± 10.84	49	0.75 ± 0.57
Insertion	53	59.51± 27.24	62	6.23 ± 6.45	61	0.66 ± 0.39
rs4802754						
CC	44	58.24 ± 27.88	50	6.82 ± 10.75	50	0.75 ±0.57
CT	37	57.02 ± 26.90	44	5.59 ± 5.41	42	0.61 ± 0.25
TT	18	62.68 ± 28.13	20	7.65 ± 8.02	20	0.78 ± 0.57
rs17526278						
CC	74	60.44 ± 27.07	88	6.88 ± 9.38	87	0.69 ± 0.46
CT	20	63.63 ± 36.13	22	6.81 ± 5.95	22	0.66 ± 0.26
TT	3	34.07 ± 7.15	3	1.47 ± 1.42	3	1.26 ± 1.54
rs266867						
AA	3	49.71 ± 18.25	3	2.34 ± 1.33	3	0.45 ± 0.11
AT	24	60.48 ± 33.75	31	6.59 ± 7.71	30	0.79 ± 0.56
TT	72	60.04 ± 28.01	80	6.68 ± 9.12	78	0.69 ± 0.46
rs266868						
AA	14	56.12 ± 27.04	14	10.89 ± 19.11	14	0.76 ± 0.72
AG	36	64.53 ± 30.18	46	5.51 ± 3.93	46	0.71 ± 0.48
GG	49	57.44 ± 28.95	54	6.29 ± 7.08	51	0.70 ± 0.42
New SNP						
CC	102	59.46 ± 29.04	118	6.64 ± 8.57	115	0.71 ± 0.48
CT	2	54.60 ± 22.48	2	4.18 ± 3.01	2	0.43 ± 10.10
TT	1		1		1	
rs2739448						
CC	22	61.65 ± 27.51	24	6.08 ± 6.02	22	0.75 ± 0.52
CT	40	58.78 ± 27.41	47	6.14 ± 6.37	46	0.63 ± 0.30
TT	37	59.90 ± 32.31	43	7.24 ± 11.63	43	0.78 ± 0.61
rs2569733						
GG	20	60.78 ± 28.41	22	5.74 ± 6.14	20	0.76 ± 0.55
GT	41	59.40 ± 27.36	48	6.26 ± 6.36	47	0.63 ± 0.30
TT	38	59.81 ± 31.88	44	7.25 ± 11.49	44	0.77 ± 0.60

PSA; prostate-specific antigen, SNP; single nucleotide polymorphism.

Table 3. Association of PSA promoter haplotype and initial serum PSA levels

Haplotype	Allele: -5217A/T SNP	Allele: -5307A/G SNP	Allele: -5412C/T SNP	Frequency	Initial PSA level ng/mL (mean±SD)	*P*	Age Years (mean±SD)	*P*
1	T	AA or AG	C	0.388	8.96 ± 11.51	0.012	70.89 ± 6.96	0.432
2	AA or AT	GG	TT or CT	0.553	4.85 ± 5.30		69.86 ± 6.75	

SNP; single nucleotide polymorphism, PSA; prostate-specific antigen.

Table 4. Pairwise test of linkage disequilibrium of SNPs in the PSA promoter area

SNP	-158	-252	-285	-5217	-5307	-5402	-5412	-5429
-158		0.88	0.63	0.72	0.45	0.19	0.52	0.60
-252			1.0	0.74	1.0	1.0	0.95	0.93
-285				0.15	0.74	0.12	0.47	0.63
-5217					1.0	1.0	1.0	1.0
-5307						1.0	1.0	1.0
-5402							1.0	1.0
-5412								0.97
-5429								

The diagonal figures represent the absolute value of Lewontin's D´.
SNP; single nucleotide polymorphism, PSA; prostate-specific antigen.

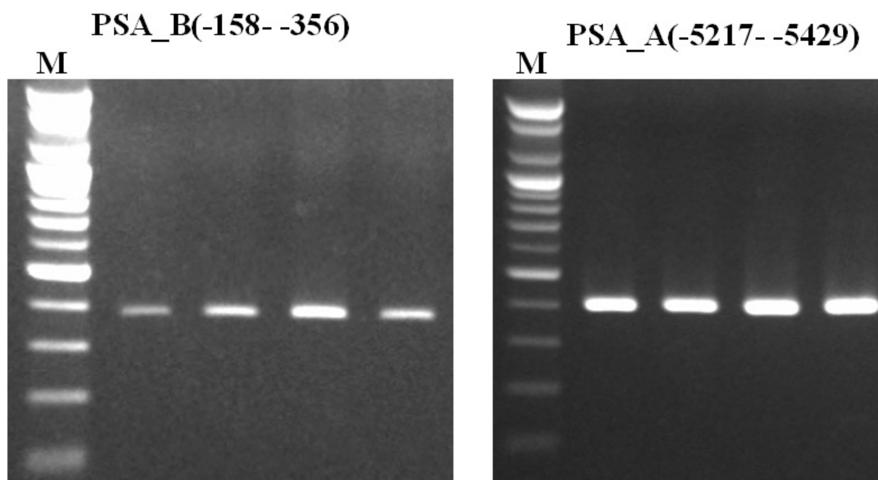

Fig. 1. The results of polymerase chain reaction. The amplified products were loaded on 2% agrose gel for 30 min under TBE (Tris base, borate, and EDTA) buffer. M: 100bp marker.

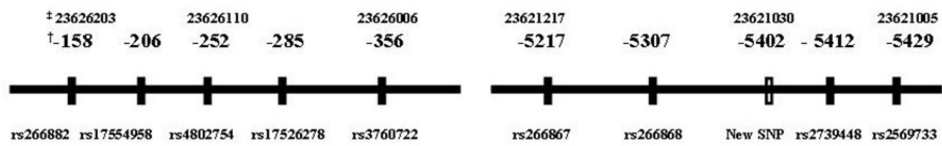

Fig. 2. Schematic structure and single nucleotide sequence polymorphisms in two prostate-specific antigen promoter area; from -158 to -356, and from -5217 to -5429 with respect to the start of transcription†, and contig positions of NT011109.15‡

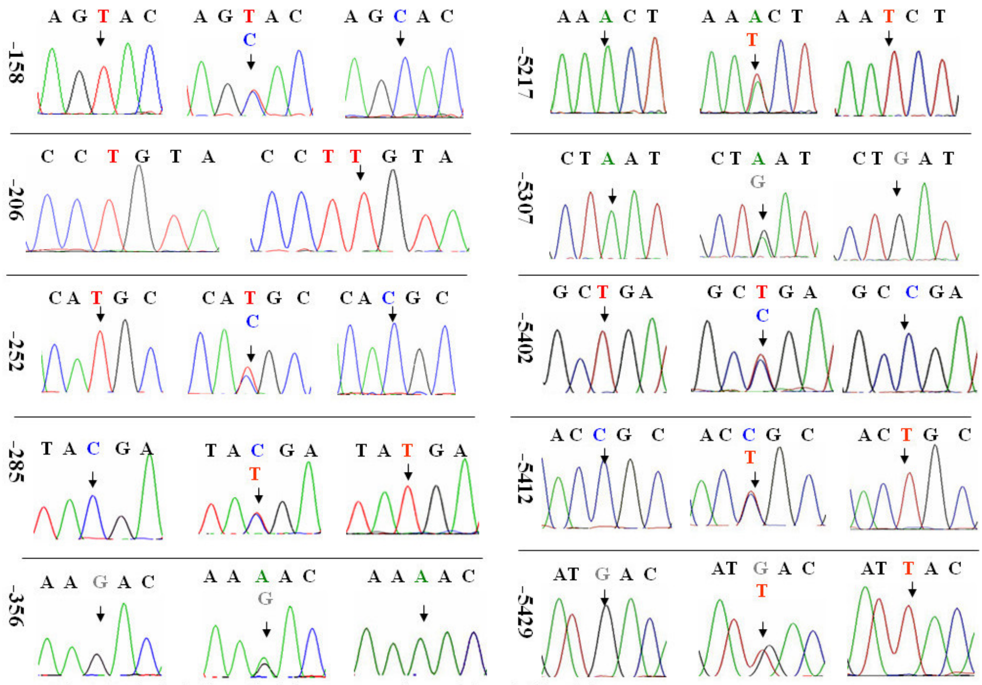

Fig. 3. Typical single nucleotide sequence polymorphisms in this study.

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저작물 이용 허락서

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논문제목	한글 : 전립선특이항원 촉진염기서열 부위에서의 유전자 다형성과 전립선비대증 표현형의 관련성에 관한 연구 영어 : The association between polymorphisms in prostate-specific antigen gene promoter and the phenotypes of benign prostate hyperplasia				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집・형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포・전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송・출력을 허락함.

동의여부 : 동의(O) 반대( )

2010 년 6 월 30 일

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