Urological Science 26 (2015) 259–266

Contents lists available at ScienceDirect

Urological Science

journal homepage: www.urol-sci.com

Original article

Polymorphisms of matrix metalloproteinases and their association with metastasis and the efficacy of androgen-deprivation therapy for prostate cancer in Taiwanese men

Cheng-Chia Lin [a], Chun-Te Wu [a], Shiang-Hsiang Huang [a], Lawrence Shih-Hsin Wu [b, *]

[a] Department of Urological Surgery, Chang Gung Memorial Hospital, Keelung, Taiwan
[b] Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan

ARTICLE INFO

Article history:
Received 10 April 2014
Received in revised form
4 November 2015
Accepted 8 November 2015
Available online 8 December 2015

Keywords:
androgen-deprivation therapy
matrix metalloproteinases
metastasis
prostate cancer

ABSTRACT

Objective: Prostate cancer is a common disease with a multifactorial and complex etiology. Genetic variants influence the level of matrix metalloproteinase (*MMP*) gene expression and protein function that are involved in susceptibility to and the prognosis of several cancers.
Materials and Methods: In this project, we selected 40 patients with prostate cancer and treated them with androgen-deprivation therapy (ADT). The prostate cancer patients treated with ADT were divided into two groups, those with a time to progression (TTP) < 12 months and those with a TTP > 12 months. The DNA from tumors (biopsy), blood, and oral epithelium cells was collected. The polymorphisms of *MMP1* -1607 1G/2G, *MMP2* -1306 C/T, *MMP3* -1171 5A/6A, *MMP8* -799 C/T, and *MMP9* -1562 C/T were selected for genotyping. The association of selected polymorphisms and prognosis of prostate cancer and efficacy of ADT were analyzed.
Results: Our preliminary results showed that *MMP2* polymorphism-associated metastasis of prostate cancer and *MMP 8* polymorphism were associated with the efficacy of ADT (defined by TTP). Furthermore, the association of *MMP8* remained significant after adjustment for other factors.
Conclusion: The promoter polymorphisms of *MMP2* and *MMP8* should be genetic markers in the prognosis and TTP of ADT in prostate cancer.

1. Introduction

Prostate cancer is the most common form of cancer among men in North America and Europe,[1] and its incidence rate has increased rapidly in Asia in the past few years.[2] Genetics and diet have been implicated in the development of prostate cancer. Many single nucleotide polymorphisms (SNPs) have been associated with the risk of prostate cancer in several genome-wide association studies, such as the Cancer Genetic Markers of Susceptibility study.[3–14] Some genetic polymorphisms are associated with the prognosis of prostate cancer.[15] However, the prognostic value of the prostate cancer-associated variants has not been well documented.

Genetic variants influence the level of matrix metalloproteinase (*MMP*) gene expression and protein function that are involved in the regulation of tumor growth and apoptosis, promotion of angiogenesis, and induction of the loss of cell adhesion, facilitating invasion, and metastasis. Inherited variation also influences the efficacy of androgen therapy.[16] A functional SNP has been reported in the *MMP1* gene promoter consisting of a guanosine (G) insertion at position −1607. This SNP generates a new 5′-GGA-3′ core recognition sequence for members of the Ets family of transcription factors; the 2G/2G genotype was reported to be linked to an increased risk of colorectal cancer.[17] A common functional polymorphism that abolishes an Sp1-binding site has been described for the promoter region of *MMP2* (−1306 C/T),[18] and the TT genotypes have been associated with a reduced risk of lung,[19] gastric,[20] and breast cancer.[21] A polymorphism was identified in the promoter region of the *MMP3* gene approximately 1600 bps upstream from the start of transcription, at position −1171, in which one allele has a run of six adenosines (6A), while the other has five adenosines (5A).[22] This polymorphism is associated with a decreased overall risk of metastasis in head/neck and breast cancer.[23] An *MMP8* -799C-T SNP was suggested in which the minor

* Corresponding author. Institute of Medical Sciences, Tzu Chi University, Number 701, Zhongyang Road, Section 3, Hualien 97004, Taiwan.
E-mail address: lshwu@mail.tcu.edu.tw (L.S.-H. Wu).

http://dx.doi.org/10.1016/j.urols.2015.11.001

alleles have reduced transcription factor binding[24] and are associated with the prognosis of breast cancer.[25,26] In the *MMP9* gene, a functional SNP (R279Q) that presumably enhances substrate binding[27,28] potentially alters the protein structure of *MMP9* and may have some functional relevance, affecting an individual's susceptibility to cancer.[29,30]

In this project, we selected 40 patients with prostate cancer, collected DNA from tumor (biopsy), blood, or oral epithelium cells, and analyzed five *MMP* genotypes using polymerase chain reaction and DNA sequencing to find causative SNPs. The potential clinical benefits of this study include finding causative SNPs and evaluating individual cancer development, metastasis, and prognosis to improve the efficacy prediction.

2. Materials and methods

2.1. Patients

A study was conducted using surgical specimens embedded in paraffin, peripheral blood mononuclear cells (PBMC), and oral swabs from 40 prostate cancer patients who received androgen-deprivation therapy (ADT) between 1999 and 2010 at the Department of Urological Surgery, Chang Gung Memorial Hospital, Keelung, Taiwan. The prostate samples were formalin-fixed and paraffin embedded, and were examined *in toto* by one uropathologist. All patients provided informed consent for their participation in the study and for their biological samples to be genetically analyzed. The study was approved by the Institutional Board of Ethics of Chang Gung Memorial Hospital.

2.2. Outcomes of ADT

All enrolled patients had been treated with ADT for non-localized, hormone-sensitive prostate cancer. Data were collected on patient and disease baseline characteristics, ADT treatment, and treatment outcome. The primary outcome variable was time to progression (TTP) during treatment with ADT. Progression was defined as two rises in the prostate-specific antigen (at least 1 month apart) greater than a nadir value while receiving ADT. These rises did not need to be sequential, but the first rise needed to be greater than the nadir prostate-specific antigen and the second rise needed to be greater than both the nadir and the first rise. The testosterone was at a castrate level (< 20 ng/dL). TTP during ADT was defined as the duration of time from initiation of ADT to the date of ADT progression or the date of initiation of secondary hormonal therapy, or was censored among patients who had not progressed at the date last known to be progression free or the date of death in patients who died without progression. The prostate cancer patients treated with ADT were divided into groups, those with a TTP < 12 months and those with a TTP > 12 months.

2.3. DNA preparation

Genomic DNA was extracted from surgical specimens embedded in paraffin, PBMCs, and oral swabs collected from 40 prostate cancer patients using a QIAamp DNA Mini Kit (QIAGEN, Valencia, CA, USA) according to the manufacturer's instructions. The extracted genomic DNA was analyzed using agarose gel electrophoresis and quantitatively determined with spectrophotometry, and stored at −80°C until use.

2.4. SNP genotyping

The polymorphisms of *MMP1* -1607 1G/2G, *MMP2* -1306 C/T, *MMP3* -1171 5A/6A, *MMP8* -799 C/T, and *MMP9* -1562 C/T were selected for genotyping. All SNP genotyping was performed using TaqMan SNP genotyping assays (ABI; Applied Biosystems Inc., Foster City, CA, USA). The primers and probes of selected SNPs were from an ABI assay on demand kit. Reactions were carried out according to the manufacturer's protocol. The probe fluorescence signal detection was performed using the ABI Prism 7900 Real-Time Polymerase Chain Reaction System (Applied Biosystems Inc.).

2.5. Statistical analysis

All association analyses between prostate cancer characters and polymorphisms were tested with the χ^2 test. Odds ratios and 95% confidence intervals were calculated from contingency tables. Other statistical analyses, including student *t* tests and the Mann–Whitney *U* test, were performed with SPSS 11.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical information on patients

The average age of enrolled patients was 79.1 ± 7.7 years (mean ± standard deviation). The clinical data of six patients including the Tumor, Node, Metastases stage and Gleason score from biopsies were not available but their metastasis statuses had been diagnosed. The Gleason score from one other patient was not available. All available clinical characteristics of the enrolled patients are listed in Table 1.

Genotyping of the DNA extracted from surgical specimens embedded in paraffin, PBMCs, and oral swabs of prostate cancer patients was performed to select *MMP* polymorphisms. The results from oral swabs and PBMCs were consistent. The DNA from some patients showed different genotyping results between cancer tissue and oral swab/PBMCs. The inconsistent genotyping results were validated with sequencing (Figure 1).

3.2. MMP3 and MMP9 putatively associated with Gleason score

The polymorphisms of *MMP3* and *MMP9* showed nominal associations with the Gleason score (Table 2). The data generated by the small sample size did not lead to a solid conclusion about which genotype was associated with a high/low level Gleason score.

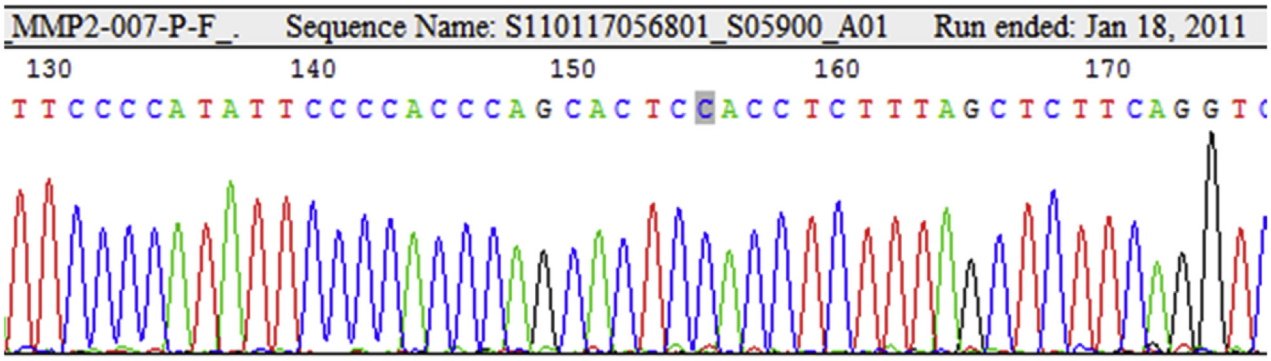
Table 1
Characteristics of the study participants.

Characteristics	Patients (*n*)
Clinical T stage at diagnosis	
T1	3
T2	10
T3	14
T4	7
Clinical N stage at diagnosis	
N0	23
N1	11
Clinical M stage at diagnosis	
M0	23
M1	11
Biopsy Gleason score at diagnosis	
6	2
7	10
8	16
9	5
Metastasis	
No	23
Yes	17

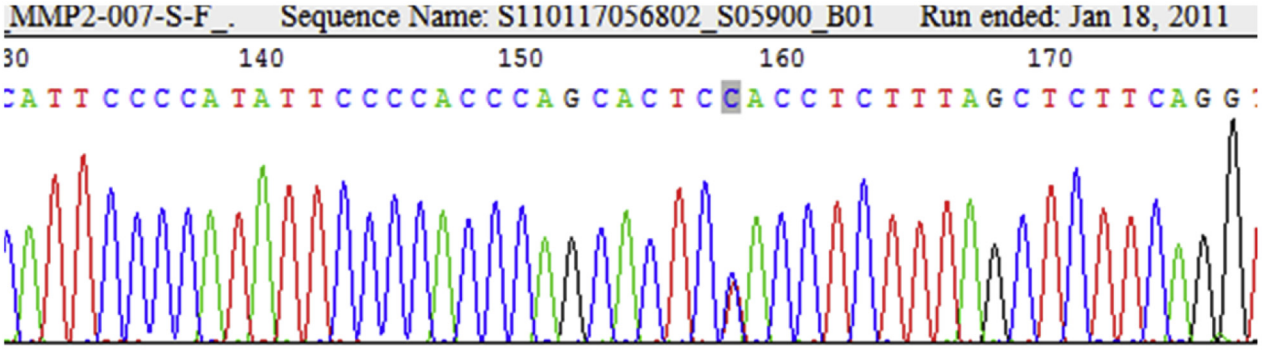
M = metastases; N = nodes; T = tumors.

MMP2 -1306C/T

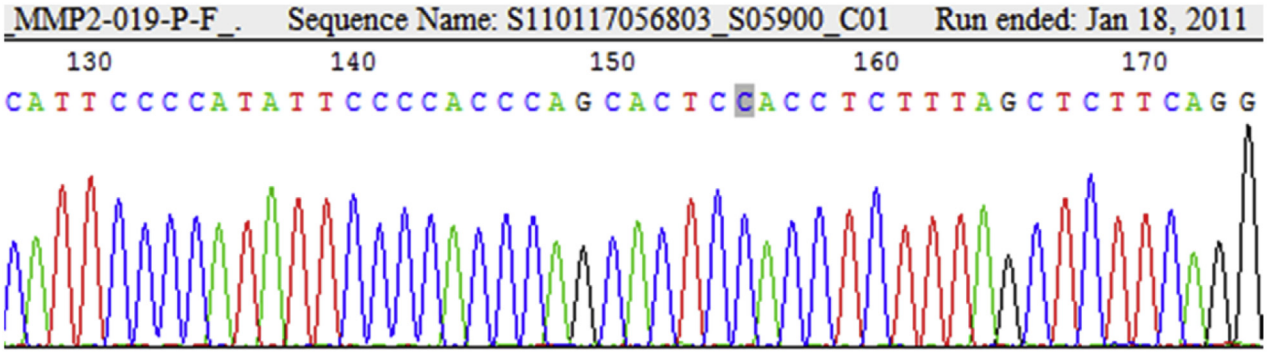
P007-P_F(C/C)



P007-S_F (C/T)



P019-P_F (C/C)



P019-S_F (T/T)

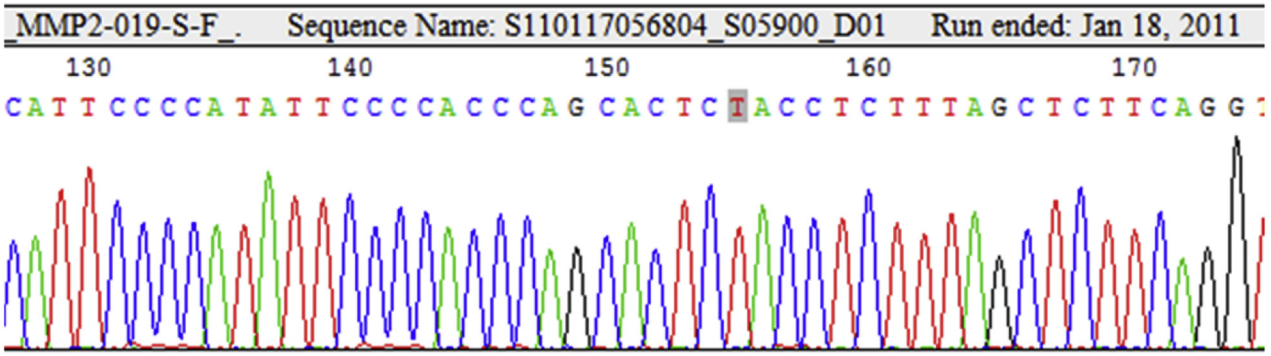
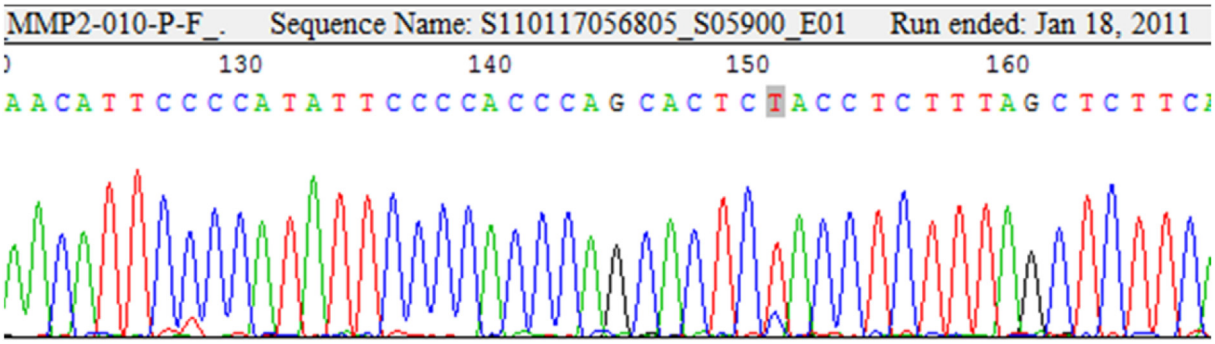
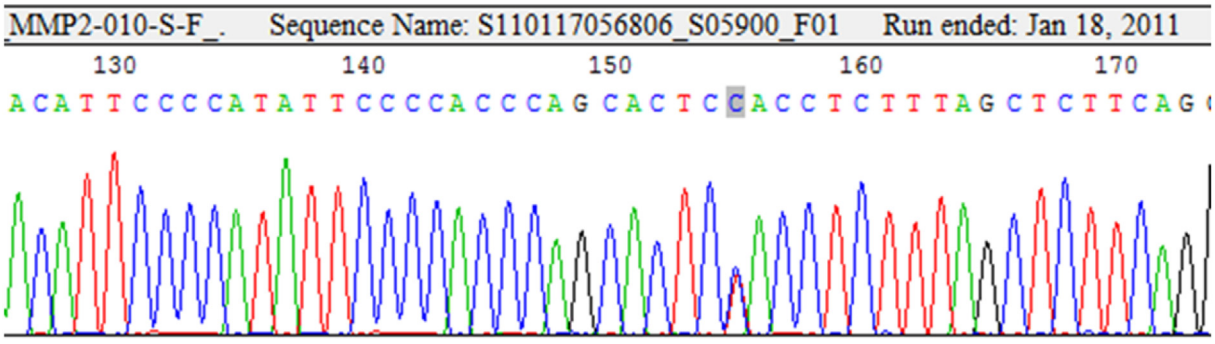


Figure 1. Sequencing of samples with inconsistent genotypes comparing DNA from peripheral blood mononuclear cells and paraffin embedded prostate cancer tissue. A = adenosine; C = cytosine; F = forward sequence; G = guanosine; P = DNA from paraffin embedded tissue; Pxxx = patient enrolled identification; R = reverse sequence; S = DNA from oral swabs; T = thymine.

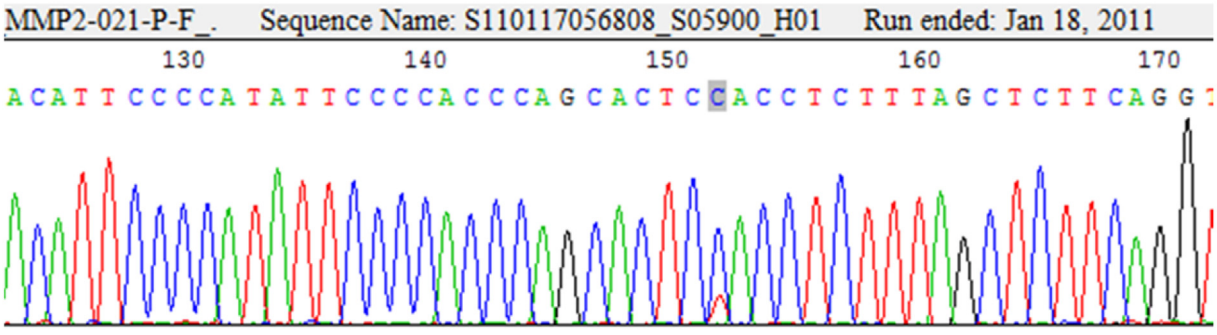
P010-P_F(T/T)



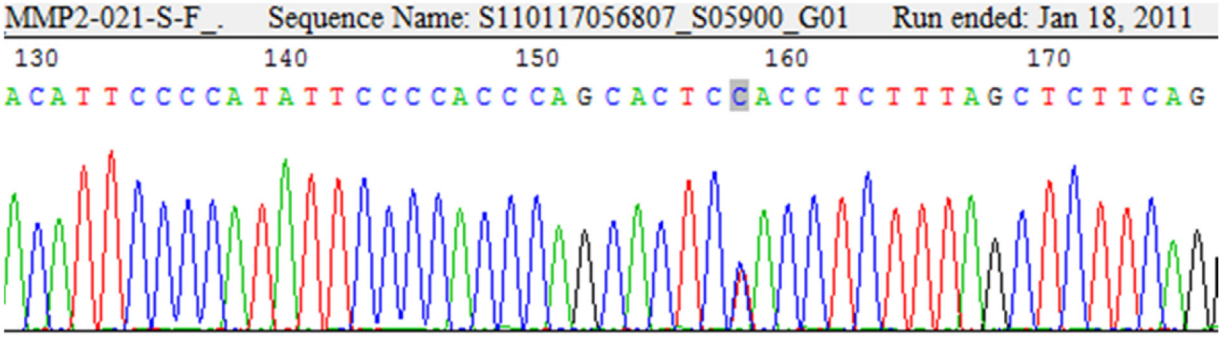
P010-S_F(C/T)



P021-P_F(C/C)



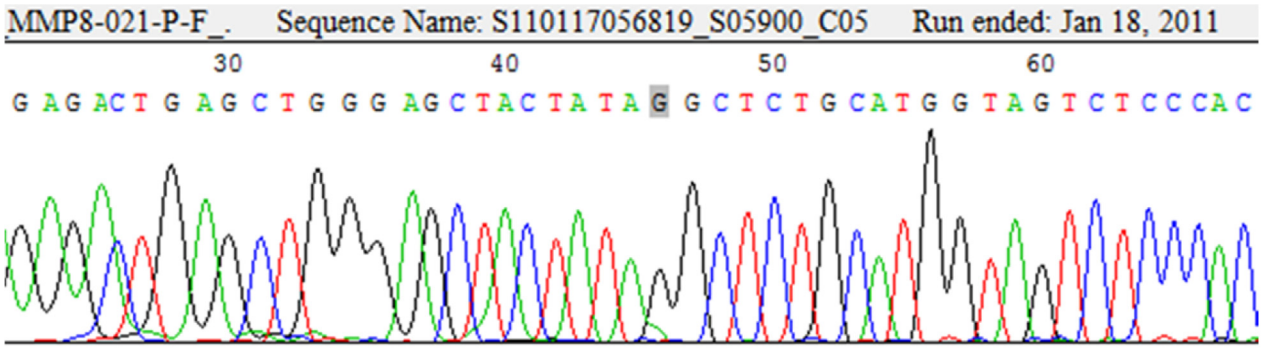
P021-S_F(C/T)



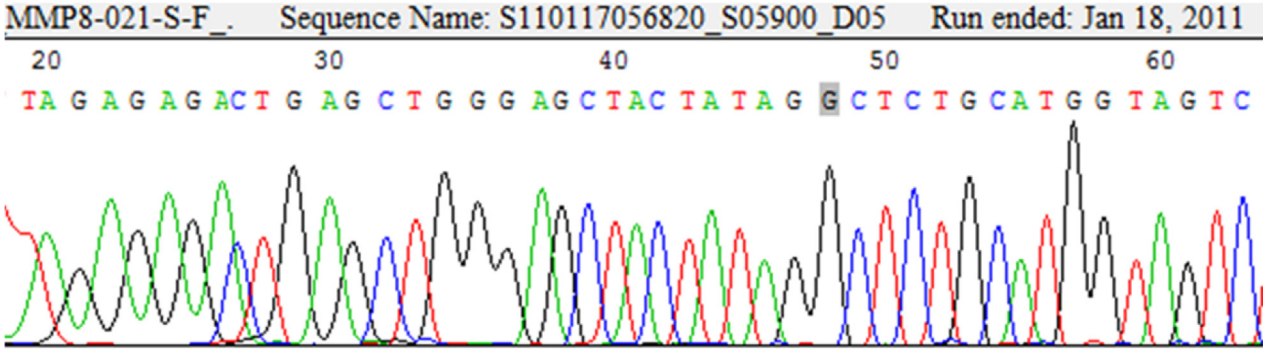
MMP8 -799C/T

P021-P_F(A/G)

Figure 1. (*continued*).

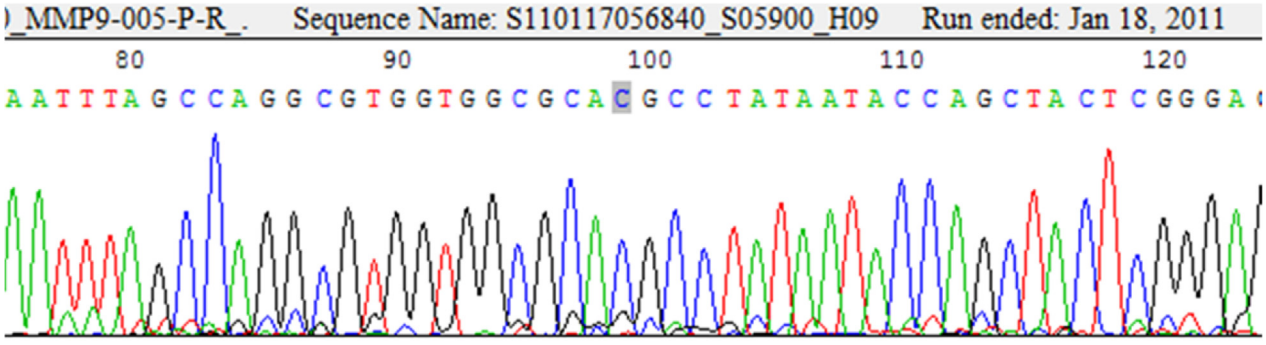


P021-S-_F(G/G)

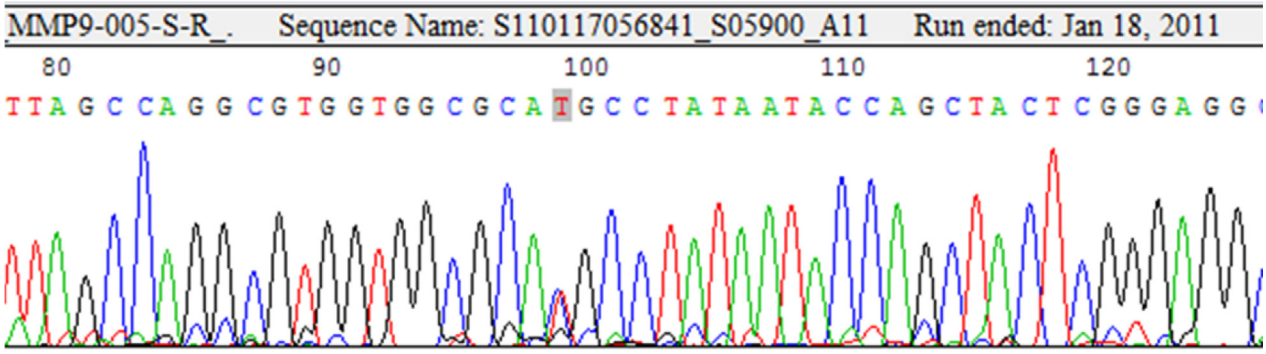


MMP9 =1562C/T

P005-P_R(C/C)

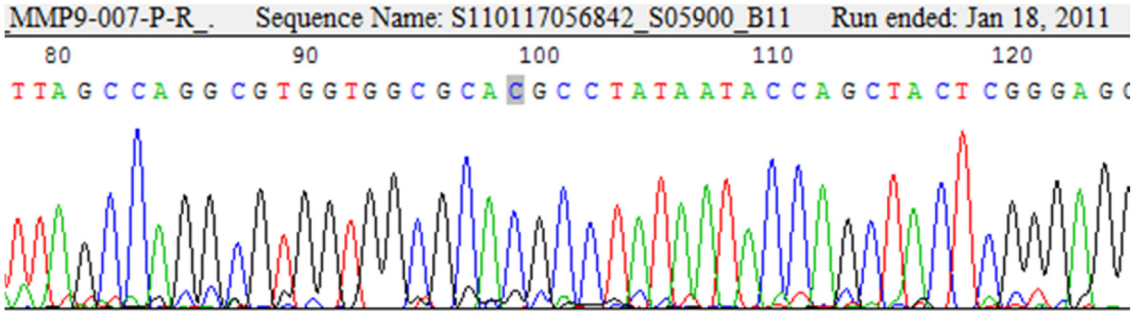


P005-S_R(C/T)

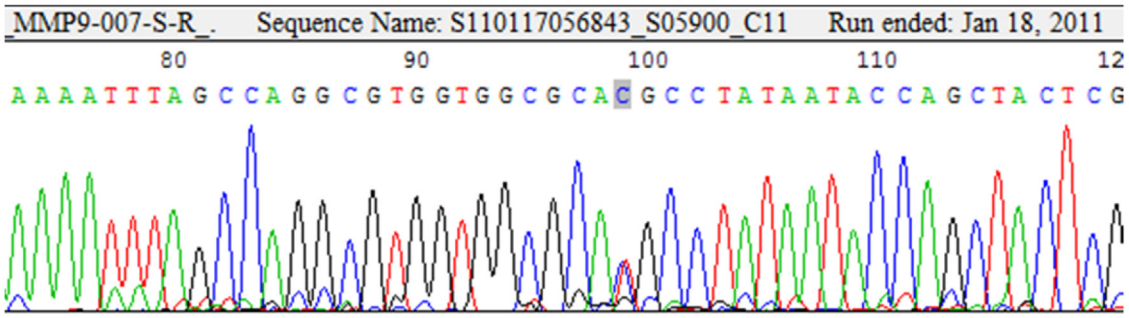


P007-P_R(C/C)

Figure 1. (*continued*).



P007-S_R(C/T)



A = adenosine; C = cytosine; F = forward sequence; G = guanosine; P = DNA from paraffin embedded tissue; Pxxx = patient enrolled identification; R = reverse sequence; S = DNA from oral swabs; T = thymine.

Figure 1. (*continued*).

3.3. *MMP2 associated with metastasis*

The polymorphism *MMP2* -1306C/T showed an association with metastasis (Table 3). Prostate cancer patients who were T carriers (CT and TT) were at a higher risk of developing metastasis than noncarriers.

3.4. *MMP8 associated with ADT efficacy*

The prostate cancer patients were divided into two groups according to the efficacy of ADT. Group 1 included 13 patients with a TTP < 12 months and an average age of 79.7 ± 7.1 years. Group 2 included 27 patients with a TTP > 12 months and an average age of 77.7 ± 9.1 years. No significant difference was found in the average age between groups ($t = 0.768$, $p = 0.447$). Five patients in Group 1 and three patients in Group 2 had metastasis. The metastasis rates in the two groups were significantly different ($\chi^2 = 4.103$, $p = 0.043$).

MMP8 polymorphism showed an association with the efficacy of ADT with the χ^2 test (Table 4). After adjusting for age and

Table 2
Genotype frequencies of matrix metalloproteinase genes by Gleason score.

Gene	Genotype	Gleason score				*p*
		6	7	8	9	
MMP1	1G/2G	2	4	8	3	0.462
	2G/2G	0	6	8	2	
MMP2	CC					
	T carrier	2	6	8	3	0.596
		0	4	8	2	
MMP3	5T/6T	2	1	6	3	0.052
	6T/6T	0	9	10	2	
MMP8	A carrier	0	7	9	2	0.283
	GG	2	3	7	3	
MMP9	CC	1	8	15	2	0.054
	T carrier	1	2	1	3	

A = adenosine; C = cytosine; G = guanosine; T = thymine.

Table 3
Genotype frequencies of matrix metalloproteinase genes by metastasis.

Gene	Genotype	No metastasis	Metastasis	*p*
MMP1	1G/1G	1	2	0.66
	1G/2G	11	8	
	2G/2G	11	7	
MMP2	CC	18	7	0.02
	CT	4	10	
	TT	1	0	
	CC (ref.) vs. T carrier	OR (95% CI)		0.02
		5.14 (1.29, 20.52)		
MMP3	5T/6T	7	7	0.48
	6T/6T	16	10	
MMP8	AA	5	3	0.60
	AG	6	7	
	GG	12	7	
MMP9	CC	17	15	0.46
	CT	5	2	
	TT	1	0	

A = adenosine; C = cytosine; CI = confidence interval; G = guanosine; OR = odds ratio; ref. = reference; T = thymine.

Table 4
Genotype frequencies of matrix metalloproteinase genes by efficacy of androgen-deprivation therapy.

Gene	Genotype	> 12 mo	≤ 12 mo	*p*
MMP1	1G/1G	1	2	0.41
	1G/2G	14	5	
	2G/2G	12	6	
MMP2	CC	19	6	0.20
	CT	7	7	
	TT	1	0	
MMP3	5T/6T	7	7	0.08
	6T/6T	20	6	
MMP8	AA	6	2	0.03
	AG	5	8	
	GG	16	3	
MMP9	CC	21	11	1.00
	CT	5	2	
	TT	1	0	

A = adenosine; C = cytosine; G = guanosine; T = thymine.

metastasis status using logistic regression, the association of *MMP8* with the efficacy of ADT remained significant (Table 5).

4. Discussion

In this case–control study, we investigated the association of SNPs in the *MMP1*, *MMP2*, *MMP3*, *MMP8*, and *MMP9* genes with metastasis, the Gleason score, and the efficacy of ADT for prostate cancer. *MMP2* -1306 C/T showed an association with metastasis of prostate cancer and *MMP8* -799 C/T was associated with the efficacy of ADT in our study population. The associations of *MMP3* and *MMP9* were weak and ambiguous because of the limited sample size. MMP polymorphisms should be clinically relevant in the prognosis of prostate cancer.

MMPs are zinc metalloproteases that degrade the collagens of the extracellular matrix important in tissue remodeling and repair during development and inflammation. MMPs may alter cell cycle checkpoint controls, may conceivably promote genomic instability by affecting cell adhesion,[31] and contribute to tumor initiation and development by altering the cellular microenvironment responsible for facilitating tumor formation.[32] A role for MMPs in angiogenesis has also been advocated.[33]

Excessive or inappropriate expression of MMPs may contribute to the pathogenesis of cancer in a wide variety of diseases by facilitating the degradation of tissues. Currently, > 20 MMPs that can be categorized by substrate specificity have been identified. Functional polymorphisms associated with characteristics of the expression of these genes may be used as genetic biomarkers in the diagnosis and prognosis of neoplasia.[34] The genotyping/sequencing results of selected polymorphisms of MMPs indicated a few inconsistent genotypes from the DNA of cancer tissues and blood/oral swabs. Some of the inconsistent genotypes should be due to the loss of heterozygosity (heterozygous in blood, homozygous in cancer tissue), and others may be due to mutations or unknown reasons. However, the observations suggest that when using MMP polymorphisms as genetic biomarkers in the diagnosis or prognosis of cancer, inconsistencies in DNA from different sources (cancer tissues and blood/oral swabs) should be noted.

Table 5
Odds ratio analysis of matrix metalloproteinase genes' genotypes by efficacy of androgen-deprivation therapy.

Gene	Genotype	> 12 mo	≤ 12 mo	*p**
MMP1	1G carrier	15	7	0.37
	2G/2G	12	6	
MMP2	CC (ref.)	19	6	0.99
	T carrier	8	7	
MMP3	5T/6T	7	7	0.12
	6T/6T	20	6	
MMP8	A carrier	11	10	0.02
	GG (ref.)	16	3	
	OR (95% CI) = 12.67 (1.06, 150.62); $p = 0.045$			
MMP9	CC	21	11	0.92
	T carrier	6	2	

**p* value was generated by logistical regression and adjusted by age and metastasis.
A = adenosine; C = cytosine; CI = confidence interval; G = guanosine; OR = odds ratio; ref. = reference genotype; T = thymine.

The *MMP2* -1306 C/T polymorphism has been associated with a reduced risk of colorectal,[35] lung,[19] gastric,[20] esophageal,[36] and breast carcinomas.[21,37] In prostate cancer, the *MMP2* -1306 C/T polymorphism was reported to be associated with the Gleason score in Brazilian men.[38] In this study, we found an association between metastasis of prostate cancer and *MMP2* -1306 C/T polymorphism. The association with prognostic characteristics, including those previously mentioned for prostate cancer should be further evaluated.

Hormonal regulation of MMPs has been observed in a variety of cells.[39] Increased *MMP* expression is generally observed in hormone-related cancers, although differences can sometimes be seen according to whether expression was studied at the transcription or translational level, or according to the location of the expression (e.g., serum or tissue). An increase in *MMP* mRNA or protein expression is almost invariably accompanied by an association with parameters of poor prognosis.[40] *MMP8* and *MMP9* alter their expression in inflammation-mediated abrogation of androgen signaling.[41] However, the mechanism or role of *MMP*s in the efficacy of ADT is largely unknown.

In conclusion, our results indicated *MMP2* -1306 C/T showed an association with metastasis of prostate cancer and *MMP8* -799 C/T was associated with the efficacy of ADT in our study population in Taiwan. It would be valuable to further investigate the clinical relevance of *MMP*s as genetic biomarkers for prostate cancer.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

Sources of funding

This study was supported by funding from Keelung Chang Gung Memorial Hospital.

Acknowledgments

Financial support was gratefully received from Keelung Chang Gung Memorial Hospital.

References

1. Crawford ED. Epidemiology of prostate cancer. *Urology* 2003;**62**:3–12.
2. Matsuda T, Saika K. Comparison of time trends in prostate cancer incidence (1973 1997) in East Asia, Europe and USA, from Cancer Incidence in Five Continents Vols IV VIII. *Jpn J Clin Oncol* 2007;**37**:556–7.
3. Al Olama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J, Severi G, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. *Nat Genet* 2009;**41**:1058–60.
4. Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, Severi G, et al. Identification of seven new prostate cancer susceptibility loci through a genome wide association study. *Nat Genet* 2009;**41**:1116–21.
5. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, et al. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 2008;**40**:316–21.
6. Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A, Agnarsson BA, et al. Genome-wide association and replication studies identify

four variants associated with prostate cancer susceptibility. *Nat Genet* 2009;**41**:1122–6.
7. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 2007;**39**:631–7.
8. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nat Genet* 2008;**40**:281–3.
9. Haiman CA, Chen GK, Blot WJ, Strom SS, Berndt SI, Kittles RA, et al. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. *Nat Genet* 2011;**43**:570–3.
10. Kote-Jarai Z, Olama AA, Giles GG, Severi G, Schleutker J, Weischer M, et al. Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study. *Nat Genet* 2011;**43**:785–91.
11. Takata R, Akamatsu S, Kubo M, Takahashi A, Hosono N, Kawaguchi T, et al. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. *Nat Genet* 2010;**42**:751–4.
12. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 2008;**40**:310–5.
13. Yeager M, Chatterjee N, Ciampa J, Jacobs KB, Gonzalez-Bosquet J, Hayes RB, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nat Genet* 2009;**41**:1055–7.
14. Yeager M, Orr N, Hayes RB, Kraft P, Wacholder S, Minichiello MJ, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet* 2007;**39**:645–9.
15. Huang SP, Bao BY, Hour TC, Huang CY, Yu CC, Liu CC, et al. Genetic variants in *CASP3, BMP5*, and IRS2 genes may influence survival in prostate cancer patients receiving androgen-deprivation therapy. *PLoS ONE* 2012;**7**:e41219.
16. Li BY, Liao XB, Fujito A, Thrasher JB, Shen FY, Xu PY. Dual androgen-response elements mediate androgen regulation of MMP-2 expression in prostate cancer cells. *Asian J Androl* 2007;**9**:41–50.
17. Zinzindohoue F, Lecomte T, Ferraz JM, Houllier AM, Cugnenc PH, Berger A, et al. Prognostic significance of MMP-1 and MMP-3 functional promoter polymorphisms in colorectal cancer. *Clin Cancer Res* 2005;**15**:594–9.
18. Price SJ, Greaves DR, Watkins H. Identification of novel, functional genetic variants in the human matrix metallo-proteinase-2 gene: role of SP-1 in allele-specific transcriptional regulation. *J Biol Chem* 2001;**276**:7549–58.
19. Yu C, Pan K, Xing D, Liang G, Tan W, Zhang L, et al. Correlation between a single nucleotide polymorphism in the matrix metalloproteinase-2 promoter and risk of lung cancer. *Cancer Res* 2002;**62**:6430–3.
20. Miao X, Yu C, Tan W, Xiong P, Liang G, Lu W, et al. A functional polymorphism in the matrix metalloproteinase-2 gene promoter (-1306 C/T) is associated with risk of development but not metastasis of gastric cardiac adenocarcinoma. *Cancer Res* 2003;**63**:3987–90.
21. Zhou Y, Yu C, Miao X, Tan W, Liang G, Xiong P, et al. Substantial reduction in risk of breast cancer associated with genetic polymorphisms in the promoters of the matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 genes. *Carcinogenesis* 2004;**25**:399–404.
22. Ye S, Eriksson P, Hamsten A, Kurkinen M, Humphries SE, Henney AM. Progression of coronary atherosclerosis is associated with a common genetic variant of the human stromelysin-1 promoter which results in reduced gene expression. *J Biol Chem* 1996;**271**:13055–60.
23. Liu D, Guo H, Li Y, Xu X, Yang K, Bai Y. Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of cancer metastasis: a meta-analysis. *PLoS ONE* 2012;**7**:e31251.
24. Wang H, Parry S, Macones G, Sammel MD, Ferrand PE, Kuivaniemi H, et al. Functionally significant SNP MMP8 promoter haplotypes and preterm premature rupture of membranes (PPROM). *Hum Mol Genet* 2004;**13**:2659–69.
25. Decock J, Long JR, Laxton RC, Shu XO, Hodgkinson C, Hendrickx W, et al. Association of matrix metalloproteinase-8 gene variation with breast cancer prognosis. *Cancer Res* 2007;**67**:10214–21.
26. Beeghly-Fadiel A, Zheng W, Lu W, Long J, Zheng Y, Cai H, et al. Replication study for reported SNP associations with breast cancer survival. *J Cancer Res Clin Oncol* 2012;**138**:1019–26.
27. Allan JA, Docherty AJ, Barker PJ, Huskisson NS, Reynolds JJ, Murphy G. Binding of gelatinases A and B to type-I collagen and other matrix components. *Biochem J* 1995;**309**:299–306.
28. O'Farrell TJ, Pourmotabbed T. Identification of structural elements important for matrix metalloproteinase type V collagenolytic activity as revealed by chimeric enzymes. Role of fibronectin-like domain and active site of gelatinase B. *J Biol Chem* 2000;**275**:27964–72.
29. Hu Z, Huo X, Lu D, Qian J, Zhou J, Chen Y, et al. Functional polymorphisms of matrix metalloproteinase-9 are associated with risk of occurrence and metastasis of lung cancer. *Clin Cancer Res* 2005;**11**:5433–9.
30. Zhang LF, Mi YY, Cao Q, Wang W, Qin C, Wei JF, et al. Update analysis of studies on the MMP-9 -1562 C>T polymorphism and cancer risk. *Mol Biol Rep* 2012;**39**:3435–41.
31. McCawley LJ, Matrisian LM. Matrix metalloproteinases: multifunctional contributors to tumor progression. *Mol Med Today* 2000;**6**:146–56.
32. Tlsty TD. Cell-adhesion-dependent influences on genomic instability and carcinogenesis. *Curr Opin Cell Biol* 1998;**10**:647–53.
33. Pattersson BC, Sang QA. Angiostatin-converting enzyme activities of human matrilysin (MMP-7) and gelatinase B/type IV collagenase (MMP-9). *J Biol Chem* 1997;**272**:28823–5.
34. Zhu Y, Spitz MR, Lei L, Mills GB, Wu X. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter enhances lung cancer susceptibility. *Cancer Res* 2001;**61**:7825–9.
35. Xu E, Lai M, Lv B, Xing X, Huang Q, Xia X. A single nucleotide polymorphism in the matrix metalloproteinase-2 promoter is associated with colorectal cancer. *Biochem Biophys Res Commun* 2004;**324**:999–1003.
36. Yu C, Zhou Y, Miao X, Xiong P, Tan W, Lin D. Functional haplotypes in the promoter of matrix metalloproteinase-2 predict risk of the occurrence and metastasis of esophageal cancer. *Cancer Res* 2004;**64**:7622–8.
37. Grieu F, Li WQ, Iacopetta B. Genetic polymorphisms in the MMP-2 and MMP-9 genes and breast cancer phenotype. *Breast Cancer Res Treat* 2004;**88**:197–204.
38. dos Reis ST, Villanova FE, Andrade PM, Pontes Jr J, de Sousa-Canavez JM, Sañudo A, et al. Matrix metalloproteinase-2 polymorphism is associated with prognosis in prostate cancer. *Urol Oncol* 2010;**28**:624–7.
39. Imada K, Ito A, Sato T, Namiki M, Nagase H, Mori Y. Hormonal regulation of matrix metalloproteinase 9/gelatinase B gene expression in rabbit uterine cervical fibroblasts. *Biol Reprod* 1997;**56**:575–80.
40. O'Mara TA, Clements JA, Spurdle AB. The use of predictive or prognostic genetic biomarkers in endometrial and other hormone-related cancers: justification for extensive candidate gene single nucleotide polymorphism studies of the matrix metalloproteinase family and their inhibitors. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:2352–65.
41. Debelec-Butuner B, Alapinar C, Varisli L, Erbaykent-Tepedelen B, Hamid SM, Gonen-Korkmaz C, et al. Inflammation-mediated abrogation of androgen signaling: an in vitro model of prostate cell inflammation. *Mol Carcinog* 2014;**53**:85–97.