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J Urol. Author manuscript; available in PMC 2014 March 03.

Published in final edited form as:
J Urol. 2008 May ; 179(5): 2020–2024. doi:10.1016/j.juro.2008.01.009.

Mismatch repair gene *MSH3* polymorphism is associated with the risk of sporadic prostate cancer

Hiroshi Hirata[1], **Yuji Hinoda**[2], **Ken Kawamoto**[1], **Nobuyuki Kikuno**[1], **Yutaka Suehiro**[2], **Naoko Okayama**[2], **Yuichiro Tanaka**[1], and **Rajvir Dahiya**[1,**]

[1]Department of Urology, Veterans Affairs Medical Center and University of California at San Francisco, San Francisco, California

[2]Department of Laboratory Medicine, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan

Abstract

Purpose—The mismatch repair (MMR) system is a DNA repair mechanism that corrects mispaired bases during DNA replication errors. Cancer cells deficient in the MMR proteins have a 10^2 –10^3-fold increase in the mutation rate. Single nucleotide polymorphisms (SNPs) of MMR genes have been shown to cause a reduction in DNA repair activity. We hypothesized that mismatch repair gene polymorphism could be a risk factor for prostate cancer (PC) and that *p53 Pro/Pro* genotype carriers could influence *MSH3* and *MSH6* polymorphisms.

Material and Methods—DNA samples from 110 cases of prostate cancer and healthy controls (n=110) were analyzed by SSCP and PCR-RFLP to determine the genotypic frequency of five different polymorphic loci on two *MMR* genes (*MSH3* and *MSH*6) and *p53* codon72. The chi-square test was applied to compare the genotype frequency between patients and controls.

Results—A significant increase in the *G/A+A/A* genotype of *MSH3 Pro222Pro* was observed in patients compared to controls (OR, 1.87; 95% CI, 1.0–3.5). The frequency of *A/G + G/G* genotypes of *MSH3* exon23 *Thr1036Ala* also tended to increase in patients (OR, 1.57; 95% CI, 0.92–2.72). Among *p53* codon72 *Arg/Pro + Pro/Pro* carriers, the frequency of the *AG + GG* genotype of *MSH3 exon23* was significantly increased in patients compared to controls (OR = 2.1, 95% CI; 1.05–4.34).

Conclusion—This is the first report on the association of *MSH3* gene polymorphisms in prostate cancer. These results suggest that the *MSH3* polymorphism may be a risk factor for prostate cancer.

Keywords

Polymorphism; mismatch repair gene; prostate cancer; *p53*

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**To whom correspondence should be addressed: Rajvir Dahiya, Ph.D., D.Sc., Professor and Director, Urology Research Center (112F), Veterans Affairs Medical Center and University of California at San Francisco, 4150 Clement Street, San Francisco, CA 94121. Phone: 415-750-6964; Fax: 415-750-6639; rdahiya@urology.ucsf.edu.

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INTRODUCTION

Prostate cancer (PC) is one of the most common malignancies in United States males.[1] Generally speaking, Japanese men have a lower incidence of prostate cancer than Americans. However recently, the prostate cancer incidence is increasing. [1] The etiology of prostate cancer is largely unknown, although several risk factors such as ethnicity, family history, and age are associated with the disease. [2] Also several dietary constituents have been linked to prostate cancer risk and prevention. [3] The mismatch repair (MMR) system is one of several DNA repair mechanisms that correct mispaired bases during DNA replication errors. Cancer cells deficient in MMR proteins have a 10^2–10^3 fold increase in their mutation rate. In the MMR system, there are seven mismatch repair genes including *MSH2*, *MSH3*, *MSH6*, *MLH1*, *PMS1*, *PMS2*, and *MLH3*.[4] The heterodimers formed by MSH2–MSH6 (MutSα) and MSH2–MSH3 (MutSβ) proteins detect mispaired bases. The MutSα complex functions to repair base-base and insertion/deletion mispairs, whereas MutSβ is associated only with the repair of insertion/deletion mispairs.[4] MutSα also associates with another heterodimer of MLH1 and PMS2 (MutLα).[4] Loss of MMR gene activity causes replication errors and thus microsatellite instability (MSI). HNPCC (hereditary non-polyposis colorectal carcinoma) is a hereditary cancer syndrome caused by *MMR* gene mutations and more than 90% of the HNPCC shows MSI.[5] Among the *MMR* genes, germ-line mutations of *MLH1*, *MSH2*, and *MSH6* have been reported in the majority of HNPCC.[5] The *MSH6* gene is on chromosome 2 and mutation of this gene has been detected in atypical HNPCC families, where the age of onset of cancer is higher than those in the usual HNPCC families.[6]

The *MSH3* gene is located on chromosome 5q11-13 and was first described in 1989.[7] The *MSH2* gene located on chromosome 2, encodes a 105 kD protein and plays a central role in mismatch recognition. Some *MSH2* SNPs are associated with a significantly increased cancer risk in endometrial, and lung cancer.[8, 9] The function of MSH3 and MSH6 overlap and apparently do not play a significant role in MMR compared to the other genes.[4]

Recently, Song et al. investigated *MMR* polymorphisms in ovarian cancer.[10] They found evidence for an increased ovarian cancer risk with SNPs in *MSH6* and *MSH3*.[10] In a previous study we showed that decreased MMR activity was associated with low expression of MMR proteins.[11] Several studies have been published associating with gastrointestinal cancer, although there have been few reports about *MMR* gene polymorphisms in prostate cancer. *p53* is a tumor suppressor gene that initiates apoptosis in response to severe DNA damage. A *p53* polymorphism at amino acid 72 (*Arg/Pro; G/C*) is very common and in an in vitro study, the *p53 Arg/Arg* genotype induced apoptosis more efficiently than the *Pro/Pro* genotype.[12] It has been thought that this genotype may be linked to decreased p53 function. Talseth et al reported an association between the *p53* polymorphism and colorectal cancer characteristics in HNPCC patients.[13] They found no association between *p53* SNPs and disease development in HNPCC patient, although there was some evidence of an effect when *MLH1* and *MSH2* mutation status was included.[13] Namely, the *p53* SNP was over-represented in a Polish *MSH2* mutation population.[13]

We hypothesized that polymorphisms of mismatch repair genes could be a risk factor for prostate cancer (PC) and that *p53 Pro/Pro* genotype carriers could influence *MSH3* and *MSH6* polymorphisms. To test this hypothesis, we examined whether polymorphisms in *MSH3* and *MSH6 genes* are associated with PC, and investigated the additional effect of *p53 Pro/Pro* on *MSH3* and *MSH6* gene polymorphisms.

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MATERIALS AND METHODS

Samples

A total of 110 patients with pathologically confirmed prostate cancer (PC), and 110 age-matched control individuals were enrolled in this study. The mean ages and standard deviation of the patient and control groups were 68 ± 5 and 68 ± 14 years, respectively (Table 1, p = 0.60). Genomic DNA was obtained from the peripheral blood of healthy controls and patients. All of the patients tested were diagnosed with prostate cancer on the basis of histopathological findings from radical prostatectomy. They were classified according to the WHO criteria and staged according to the tumor-node-metastasis (TNM) classification and the Gleason grading system. Healthy controls consisted of volunteers with no apparent abnormal findings upon medical examination at Shimane University Hospital.

Regarding body mass index (BMI), the frequency of more than 23 kg/m^2 was 60% and 58% in PC cases and controls, respectively. There was no statistical difference between the two groups (p=0.89). The smoking statuses were investigated through interviews with doctors or nurses. Current smokers were defined as those who smoked within 12 months of tumor development. Former smokers were those who had quit smoking more than 12 months before tumor development. None of these patients had received androgen deprivation therapy before radical prostatectomy. There were no significant differences between patients and control groups with regard to family history of cancer.

Genotyping

Polymorphisms were analyzed by SSCP (Single Strand Conformational Polymorphism) or PCR-RFLP. Primer sets and annealing temperatures used for SSCP and RFLP are shown in Table 2. PCR products were digested with *BstuI* (New England Biolabs, Beverly, MA) for *p53.* The restricted products were analyzed in a 2% agarose gel containing ethidium bromide. SSCP was performed using non-radioactive method. To confirm the genotype ascribed by SSCP or RFLP, the PCR products were subjected to direct sequencing. The reaction products were analyzed using an ABI PRISM 377 DNA sequencer (Applied Biosystems).

Statistical analysis

Hardy-Weinberg equilibrium was evaluated using SNPAlyze version 2.2 (DYNACOM Co. Ltd., Tokyo, Japan). The strength of associations between PC patients and MMR gene polymorphisms were measured as odds ratios (ORs). The ORs were obtained with unconditional logistic regression analysis. Crude ORs and those adjusted for age were calculated. All statistical analyses were performed using StatView (version 5; SAS Institute Inc., NC). A *p*-value of less than 0.05 was regarded as statistically significant.

Results

Characteristics of pc patients and controls

Table 1 shows the mean age, pT, Gleason sum, preoperative serum PSA, and smoking status of individual PC patients. Two-tailed Student's *t*-tests were used to compare the age distribution between patients and control subjects. There was no significant difference of mean age between cases and controls (Table 1). In the 110 prostate cancer cases, 67 (61%) were organ confined and 71 (64%) had a Gleason sum (GS) of less than 7.

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Hardy-Weinberg equilibrium

The genotype frequencies of the four polymorphisms in total samples (n = 220), PC patients (n = 110) and healthy controls (n = 110) were consistent with the Hardy-Weinberg equilibrium distribution (*p*-value > 0.05).

MSH3 and MSH6 gene polymorphism and pc

Table 3 shows the genotype distribution of the *MSH3 Pro222Pro* (rs1805355), *MSH3 Thr1036Ala* (rs26279), *MSH6 rs1042821*, *MSH6 rs3136245* polymorphisms in PC cases and healthy controls. A significant increase in the *G/A + A/A* genotypes of *MSH3 Pro222Pro* was observed in patients compared to controls (OR, 1.87; 95%CI, 1.0–3.5; p = 0.04) (Table 3). The frequency of *A/G + G/G* genotypes of *MSH3* exon 23 *Thr1036Ala* also tended to increase in patients (OR, 1.57; 95%CI, 0.92–2.72; p = 0.09). There was no statistical difference in the genotypes of the *MSH6 rs1042821* and *MSH6 rs3136245* polymorphisms between cases and controls. The frequencies of the variant alleles between cases and controls were as follows: *MSH3 Pro222Pro* (45%, 38%), *MSH3 Thr1036Ala* (26%, 20%) *MSH6 rs1042821* (35%, 34%) and *MSH6 rs3136245* (54%, 55%) (Table 3).

Relationship of the MSH3 exon4 polymorphism with clinical parameters in pc patients

The relationship of *MSH3 exon4* polymorphisms with clinicopathological parameters including age at onset, Gleason sum, pT, and smoking status in PC patients was evaluated. There was no statistically significant association of the *MSH3 exon4* genotypes with these parameters (data not shown). We also found no association between smoking status and the MSH3 polymorphism.

The effect of both p53codon72 polymorphism and MSH3 and MSH6 polymorphisms in pc patients

Among *p53* codon72 *Arg/Pro+Pro/Pro* carriers, the frequency of the *G/A+A/A* genotype of *MSH3 exon4* tended to increase in PC patients compared to controls (OR, 1.78; 95%CI, 0.79–4.02; p = 0.16). With regard to *MSH3* exon23, a significant increase in the *AG+GG* genotype of *MSH3 exon23* was observed in patients compared to controls (OR, 2.1; 95%CI, 1.05–4.34; p = 0.04) (Table 4).

Discussion

In the eukaryotic MMR system, mispaired DNA bases are recognized by heterodimeric complexes including MSH2–MSH3 (MutSβ) and MSH2–MSH6 (MutSα). MSH2 has a central role in DNA recognition. Prtilo et al.[14] investigated MSH2 expression with respect to Gleason sum and survival of prostate cancer. They reported that higher Gleason sum correlated with higher MSH2 expression and low MSH2 expression correlated with prolonged survival.[14] However Chen et al observed a reduction of MSH2 protein in prostate cancer compared to normal adjacent prostate tissue.[15] This discrepancy may be caused by mutation status or other reasons.

MSH3 and MSH6 proteins form a complex with MSH2 that binds to DNA mismatches, initiating strand-specific repair of DNA replication errors.[16] Umar et al observed that transfection of MSH3 or MSH6 protein into a human tumor cell line corrected instability at the microsatellite loci and restored MMR activity.[16] Therefore MSH3 and MSH6 may complement the MMR system independently. Many of the *MMR* gene polymorphism studies have focused on HNPCC (hereditary non-polyposis colorectal carcinoma). With regard to *MSH3* gene polymorphisms, Orimo et al. found a frameshift mutation in sporadic colon cancer.[17] They also found three SNPs in the *MSH3* gene and frequency of the *G693*

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(*G/A*) allele was high in sporadic colon cancer patients.[18] Song et al systematically investigated all the common genes in the MMR system and confirmed the effect of SNPs on ovarian cancer risk. In their study, *MSH3* SNPs were not associated with the risk of ovarian cancer.[10] This is the first case-control study to investigate the relationship between *MSH3* and *MSH6* polymorphisms and prostate cancer susceptibility. In our study, the *MSH3* exon4 SNP does not result in an amino acid substitution in the protein sequence, although it was significantly associated with the susceptibility of prostate cancer (OR, 1.87; 95%CI, 1.00–3.50). The frequency of *MSH3* exon23 *A/G* + *G/G* genotype also tended to be higher in prostate cancer patients (OR=1.57; 95% CI: 0.92–2.72). In addition, we investigated the relationship between *MSH6* rs1042821 *G/A* and rs3136245 *C/T* SNPs and prostate cancer risk, but found no evidence supporting an association. Several studies have investigated the effect of the *p53* codon72 polymorphism. Suzuki et al. found a significant association between the *p53 Arg72Pro* polymorphism and prostate cancer risk in Japanese.[19] Although Henner et al. found a decreased risk for this same polymorphism in Caucasians.[20] One possible explanation for this discrepancy is the effect of racial differences. We demonstrated that the frequency of the *Arg/Pro+Pro/Pro* genotype of *p53 Arg72Pro* tended to increase in PC patients compared to controls (OR = 1.35, 95%CI = 0.78–2.34) suggesting that the *p53* codon72 polymorphism alone might not influence prostate cancer risk.

We also examined the added effect of the *p53 Arg72Pro* polymorphism on *MSH3* and *MSH6* polymorphisms on prostate cancer risk. Among *p53 Pro/Pro* + *Arg/Pro* genotype carriers, the frequency of *MSH3* exon23 *AG* + *GG* genotypes is significantly higher in PC patients (OR = 2.1, 95%CI = 1.05–4.34, p=0.04). Such an effect was not observed between *p53 Arg72Pro* and *MSH3* exon4 *G/A* (OR = 1.8, 95%CI = 0.79–4.02, p=0.16). In conclusion, this is the first report to show an association of *MSH3* gene polymorphisms in PC. In addition the *p53* codon 72 polymorphism may increase the risk of the *MSH3* polymorphism for prostate cancer.

Acknowledgments

We thank Dr. Roger Erickson for his support and assistance with the preparation of the manuscript. This study was supported by Grants RO1CA101844, RO1AG21418, R01CA111470, R01CA108612, T32-DK07790 from the NIH, VA REAP award, Merit Review grants (PI: Rajvir Dahiya), and Yamada Science Foundation.

Abbreviations and acronyms

PCR	polymerase chain reaction
RFLP	restriction fragment length polymorphism
SNP	single nucleotide polymorphism

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Table 1

Characteristics of PC patients and controls

	Cases (n=110)	Controls (n=110)
Age(mean ± S.D.)[a]	68±5	68±15
pT		
1	0 (0%)	
2	67 (61%)	
3	39 (35%)	
4	4 (4%)	
Gleason sum		
<7	71 (64%)	
7	23 (21%)	
>7	16 (15%)	
Preoperative serum PSA		
<4	18 (16%)	
4–10	53 (48%)	
>10	36 (36%)	
Smoking status		
Yes (current and former smokers)	48 (44%)	
No (never smokers)	62 (56%)	

[a] Cases versus controls, $P = 0.60$

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Table 2

Primer sequence and annealing temperature

	primer sequence	annealing T(C)	PCR product	genotyping
MSH3 codon222	S 5 -AAAACTTTATACATCTTTTGGTTGC -3′	53	178 bp	**SSCP**
rs1805355	AS 5 -ACTGCATCTTTGTGCTGCTG -3′			
MSH3 codon1036	S 5 -TTTCAGCTTTCAGGCACAGTT -3′	57	200 bP	**SSCP**
rs26279	AS 5 -CCTTCCAGCTCTTTTGACTTG -3′			
MSH6 codon39	S 5 -AGCTTCTTCCCCAAGTCTCC -3′	56	205 bp	**SSCP**
rs1042821	AS 5 -CCCTCCGTTGAGGTTCTTC -3′			
MSH6 intron 2	S 5 -TTGTTTAAGCGACCCTTTCC -3′	56	176 bp	**SSCP**
rs3136245	AS 5 -ATACACCCGTTTGGTTTGGA -3			
p53 codon72	S 5 -TTGCCGTCCCAAGCAATGGATGA -3′	56	199 bp	**RFLP (BstU I)**
	AS 5 -TCTGGGAAGGGACAGAAGATGAC -3			

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Table 3

Distribution of MSH3 and MSH6 gene polymorphisms in PC patients and controls

Gene	Genotype	Cases (n=110) (%)	Controls (n=110) (%)	Age adjusted OR	95%CI	P-value
MSH3						
exon4 (G/A)	G/G	21 (19)	34 (31)			
	G/A	78 (72)	69 (63)			
	A/A	11 (10)	7 (6)	1.63	0.61–4.39	0.44
	G/A + A/A	89 (81)	76 (69)	1.87	1.00–3.50	0.04
	G allele	120 (55 %)	137 (62 %)			
	A allele	100 (45 %)	83 (38 %)	1.33	0.76–2.34	
MSH3						
exon23 (A/G)	A/A	60 (55)	72 (65)			
	A/G	43 (39)	31 (28)			
	G/G	7 (6)	7 (6)	1.00	0.34–2.95	
	A/G + G/G	50 (45)	38 (34)	1.57	0.92–2.72	0.09
	A allele	163 (74 %)	175 (80 %)			
	G allele	57 (26 %)	45 (20 %)	1.34	0.86–2.10	
MSH6						
exon1 (G/A)	G/G	44 (40)	46 (42)			
	G/A	55 (50)	54 (49)			
	A/A	11 (10)	10 (9)	1.11	0.45–2.73	0.82
	G/A + A/A	66 (60)	64 (58)	1.10	0.63–1.85	0.78
	G allele	143 (65 %)	146 (66 %)			
	A allele	77 (35 %)	74 (34 %)	1.06	0.72–1.57	
MSH6						
Intron 2 (C/T)	C/C	16 (15)	20 (18)			
	C/T	69 (62)	59 (54)			
	T/T	25 (23)	31 (28)	0.75	0.41–1.38	0.35
	T/T + C/T	94 (85)	90 (82)	1.31	0.64–2.67	0.46
	C allele	101 (46 %)	99 (45 %)			
	T allele	119 (54 %)	121 (55 %)	0.96	0.66–1.40	

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Table 4

(a) p53 genotyping (b) Association of the MSH3 MSH6 polymorphisms in the *p53 Arg/Pro+Pro/Pro*

(a)

Genotype *p53 Arg/Pro*	Cases(n=110) *n*(%)	Controls(n=110) *n*(%)	Crude OR (95%CI)
Arg/Arg	39 (35.0 %)	47 (43.0 %)	
Arg/Pro	59 (54.0 %)	49 (45.0 %)	
Pro/Pro	12 (11.0 %)	14 (12.0 %)	0.84 (0.37–1.91)
Arg/Pro+Pro/Pro	71 (65.0 %)	63 (57.0 %)	1.35 (0.78–2.34)

(b)

	p53 Arg/Pro+Pro/Pro		Crude OR (95% CI)	*p*-value
	Case (n=71)	Control (n=63)		
MSH3 ex4				
GG	13 (18)	18 (29)		
GA+AA	58 (82)	45 (71)	1.78 (0.79–4.02)	0.16
MSH3 ex23				
AA	37 (52)	44 (70)		
AG+GG	34 (48)	19 (30)	2.1 (1.05–4.34)	0.04
MSH6 ex1				
GG	28 (39)	26 (41)		
GA+AA	43 (61)	37 (59)	1.1 (0.54–2.15)	0.83
MSH6 int2				
CC	10 (14)	11 (17)		
CT+TT	61 (86)	52 (83)	1.3 (0.51–3.28)	0.59