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SNPs associated with prostate cancer risk and prognosis

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1. ABSTRACT

Studies of the genetic influences on prostate cancer have indicated that there are familial genes that account for only a small fraction of the genetic components of prostate cancer. Many investigators have investigated the association of single nucleotide polymorphisms in candidate genes with an increased risk in prostate cancer. The types of candidates examined include genes in steroidmetabolism, oxidative stress, and DNA repair as well as common variants of genes found by family studies. These analyses have identified some SNPs that are associated with prostate cancer risk. A complete genetic snapshot of prostate cancer risk will only be obtained when all the genetic risk factors are identified and combined with other known markers of risk.

2. INTRODUCTION

Prostate cancer is the most common cancer of men in the United States, but the cancer mortality of this disease is now decreasing because of earlier detection and improved therapy. Despite the frequency of the disease, the genetic mechanisms involved in the pathogenesis and progression of prostate cancer remain to be identified. Prostate cancer family studies have not identified strong genes in prostate cancer. Part of this inconclusiveness maybe related to variable penetrants, genetic polymorphisms or epigenetic confounders. Three genes have been isolated that are associated with a susceptibility to prostate cancer. ELAC2 (1) or HPC2 is a candidate tumor suppressor gene on chromosome 17 identified by linkage studies. Although the functional significance of this gene in the pathogenesis of prostate cancer is unknown, the gene codes for a protein involved in RNA processing (2). A second, potential gene involved in RNA metabolism that is a prostate cancer gene is RNASEL (ribonuclease L) on chromosome 1p25 (3). Specific RNASEL genotypes may act in concert with an infectious agents as suggested by the work of Urisman (4). Macrophage scavenger receptor (MSR1) on chromosome 8p22 also linked in family studies suggests that it is a potential susceptibility factor. Several other genes have been implicated in prostate cancer and include BRCA 1 and BRCA2 (5, 6) and CHEK2 (7, 8, 9).

An historical Scandinavian twin study estimated that 42% of prostate cancer risk can be attributed to genetic factors (10). The complexity of analyzing genes is related to multiple genetic interactions and multiple undefined endogenous and exogenous risk factors in relation to the microecosystem of the host. Considering these confounders, it is estimated that identified genes in loci only account for 5-10% of genetic factors. Now with the availability of high throughput SNP analysis, there has been an intense effort to identify common polymorphisms that contribute to the genetic susceptibility of prostate cancer. The initial SNP analysis has focused on previously identified candidate genes. There are several broad categories of genes and they include: genes in steroid metabolism, defined tumor suppressor genes, genes related to oxidative stress, DNA repair genes, and genes regulating angiogenesis. Many of the variants studied are single nucleotide polymorphisms (SNPs). This chapter will focus on SNPs defined in prostate cancer. Interestingly, a polymorphism in the transmembrane serine protease 2 (TMPRSS2) gene was found to be associated with prostate cancer risk in 2004 (11). Subsequent to this finding, TMPRSS2 was identified as a fusion partner with the ETS transcription factor family members (ERG, ETV1, and ETV4) a common set of translocations in prostate cancer (12, 13, 13, 13).

3. STEROID METABOLISM

3.1. The Androgen Receptor (AR)

The androgen receptor gene is a major gene that may be relevant to prostate cancer risk. There are two triplet repeats in the androgen receptor. A CAG repeat in the first exon results in an expansion of a polyglutamine tract. A second repeat of GGC results in a polyglycine expansion. Many groups have studied the CAG repeat in different populations. The general observation is that a lower number of CAG repeats is associated with prostate cancer risk and early age of onset (see Table 1). The number of repeats used as a cut off for defining cancer risks has varied significantly in representative studies and the importance of the number of repeats has not been confirmed in all studies. For those studies reporting a statistically significant odds ratio (OR), a lower number of CAG repeats was associated with an OR of 1.2 to 3 (see references in Table 1). One study reported that Japanese man have prostate cancer risk associated with a greater number of repeats as opposed to a Swedish men who showed an association with fewer repeats (14). All other populations showed a trend for an increased risk of prostate cancer associated with fewer CAG repeats (see Table 1). A lower number of repeats in the GGC tract has been associated with prostate cancer risk in some cases (15, 16).

3.2. Steroid 5 alpha reductase (SRD5A2)

Steroid 5 alpha reductase is an important enzyme which converts testosterone to dihydrotesterone in the prostate. Many of the nonsynonymous coding variants of SRD5A2 influence the function of this enzyme which converts testosterone to dihydrotesterone (17). Several SNPS of this enzyme have been examined for an association with prostate cancer (see Table 1). The variant V89L has modest significance as a risk factor with OR in the range of 1.5-1.8 (18, 19, 20, 21) in those studies that found an association. Cicek *et al* (20) indicated that the polymorphism may be associated with an earlier diagnosis (OR = 2.35, $p < 0.001$) or more aggressive disease (OR = 1.63, $p = 0.06$).

3.3. Cytochromes

Several cytochrome p450 molecules have been implicated in prostate cancer. SNP analysis of CYP17 has been studied by several groups because of its role in androgen synthesis. Multiple studies have resulted in variable conclusions, but meta analysis performed by Ntais *et al* (22) indicated that the CYP17 polymorphism is significant in the African American population [OR for A2 1.56 (CI 1.07, 228)], but not the Asian or Caucasian populations. Very significant results have been observed with haplotypes of CYP17 with CYP3A4 (23) or CYP3A4 and CYP3A43 (24). It might be anticipated that high odds ratios would be observed for enzymes involved in the reduction of oxidative stress. Odds ratios have exceeded 5 for the combinationof CYP3A4*1B and CYP3A43 (24).

3.4. Hydroxy-delta-5-steroid dehydrogenase, 3 (HSD3B) and hydroxysteroid (17-beta) dehydrogenase (HSD17B)

A significant association of HSD3B1 and HSD3B2 with prostate cancer risk was found by Chang *et al* (25). A nonsynonymous polymorphism in the HSD17B3 locus of G287S had a 2.5 fold risk as determined by Margiotti *et al* (26).

Table 1. Examples of SNP association studies in prostate cancer

Androgen Metabolism					
Androgen Receptor (AR)					
AR	CAG	Japanese	88sporadic53 controls	p = 0.026 for association of repeats with response to therapy	118
	CAG	Finnish	105 HPC 461 sporadic 223 BPH 574 controls	short repeat < 18 OR 1.47 (p= 0.05)	119
	CAG	Caucasian Afr. Amer.	40 sporadic	weak risk factor	120
	CAG	Hispanics	82 sporadic 175 controls	<18 repeats OR 2.7 (1.21, 6.01)	121
	CAG	Indian	113 sporadic 133 controls	<22 repeat associated with risk (OR = 2.96) <22 repeats associated with young age of onset (2.18)	122
	CAG	Caucasian	288 sporadic 700 controls	<22 lower early onset PrCa (OR 0.68, 0.50, 0.91)	19
	CAG	Caucasian Afr. Amer.		>24 Longer survival	123
	CAG	meta analysis		1.19 (1.07, 1.31) fewer repeats associated with PrCa	16
	CAG	Swedish and Japanese	388 sporadic 98 controls 33 sporadic 43 controls	Swedish shorter CAG assoc. with PrCa Japanese longer CAG	14
	CAG	Caucasian	591 sporadic 591 controls	Short repeat OR 1.52 (0.92, 249)	124
	CAG	Brazilian	133 sporadic 279 controls	no association with risk, assoc young age of onset	125
	CAG	Caucasian	265 sporadic	no association	126
	CAG	Caucasian	190 sporadic 190 controls	no association	41
	CAG	Afr. Amer.	21 sporadic 19 controls	no association	127
	CAG	Chinese	66 sporadic 104 controls	no association with repeat	128
	CAG	multi-ethnic	2036 sporadic 2100 controls	no association	129
	CAG or GGC	Caucasian	591 sporadic 538 controls	no association with repeat length	130
	GGN	meta analysis		1.31 (1.06, 1.61) lower repeats associated with PrCa	16
	GGC	86% Caucasian 7% Afr Amer	159 HPC 245 sporadic 222 controls	< 16 repeats associated with PrCa	15
	E211 G>A		815 sporadic 719 controls	A is at risk for metastatic PrCa	131
Estrogen receptor					
ER Beta	rs3829768* rs1271572* rs3841304 rs1256049 (exon 7)	Asian	40 sporadic 86 controls	*Associated with PrCa	31
ER alpha	(GGGA)n	Caucasian	294 sporadic 296 controls	5/5 repeats OR 4.6 (0.99, 21.67)	32
ER alpha	T10C	Japanese	45 sporadic 200 controls	CC associated with OR 3.26 (1.58, 6.73)	33
HSD3B1 HSD3B2		84%Caus, 8.8% Afr Amer	159 HPC 245 sporadic 222 controls	B1 N367T or B2C751g associated with PrCa	25
HSD17B3	G287S	Caucasian	103 sporadic 109 controls	OR 2.5 (1.03, 6.07)	26
A1B1/SRC3 Amplified in breast cancer	CAG/CAA repeat	Chinese	189 sporadic 301 controls	<29 repeats OR 1.81 (1.00, 3.87)	132
CYP1A	Val/Val	Turkish	100 sporadic 107 controls	OR 2.846 (1.00, 8.05)	133
CYP1A1	Haplotypes		159 HPC 245 sporadic 222 controls	TAC increased in PrCa CAC decreased in PrCa	134
CYP1A1	Val	Japanese	115 sporadic 200 controls	Val/Val OR 2.4 (1.01, 5.57)	135
CYP1A1	MspI	Caucasian	288 sporadic 700 controls	no association	19
CYP1B1	Codon 119	Japanese	117 sporadic 200 controls	4.02 (1.73, 6.05)	136

CYP2E	DraI	Caucasian	103 sporadic 123 controls	DD 2.12 (1.11,4.03)	137
CYP3A4*1B		Caucasian Afr Amer	622 sporadic 396 controls	0.54 (0.32, 0.94)	138
CYP3A4*1B CYP3A43	Haplotype	Caucasian Afr Amer	622 sporadic 396 controls	5.86 (1.10, 31.16)	24
CYP3A5	A6986G	Japanese	260 sporadic 212 controls	AA OR of 0.23 for low grade	139
CYP11A1	(tttta)n (5bp repeat)	Japanese	278 sporadic 213 BPH 299 controls	1.76 (1.08, 2.97)	140
CYP17	5 promoter polym	Brazilian	92 sporadic 200 controls	no association	141
CYP17	MboI	Afr Amer Caucasian	84 sporadic 136 controls 77 sporadic 82 controls	TT OR 2.8 (1.0, 7,4)	142
CYP17		Japanese	105 sporadic 210 controls	A2A2 OR 2.39 (1.04, 5.46)	143
CYP17A1	haplotyped with CYP3A4	90% Cauc 10% Afr Amer	440 sporadic 480 controls	significance with specific haplotypes	23
CYP17	A2		600 sporadic 590 controls	OR 1.23 (0.99, 1.54)	144
CYP17	2 variants	Eur. Cauc		no association	145
CYP17	MspI promoter	Turkish		no association	146
CYP17	A1/A1 or A1/A2 with GSTP1 Ile/Val with PON1 QR, LM-MM	Italian	384 sporadic 360 controls	increased risk	147
CYP17	meta analysis	Afr Amer Caucasian Asian		A2 1.56 (1.07, 228) no association no association	22
CYP19	Tetramer	91% Cauc 8% Afr Amer	439 sporadic 479 controls	no association	148
CYP19	(ttta)n	Japanese	99 HPC 110 controls	Short A1 1.43 (0.96, 2.14) A1A1, A1A2, A2A2 OR 1.8 (1.4, 2.11)	149
PON1	I102V	Finnish	69 sporadic 69 controls	V OR 6.3 (2.1, 19.2) VV OR 4.3 (0.9, 21.5)	150
SRD5A2	A49T	Finnish	449 sporadic 223 BPH 588 controls	no association	151
SRD5A2	LL A49T	Japanese	105 sporadic 210 BPH	no association	143
SRD5A2	V89L	Japanese	302 sporadic 228 BPH 243 controls	LL has OR 1.69 (1.07, 2.65)	18
SRD5A2	(A49T, V89L, 682G)	Caucasian Ashkenazi Afr Amer	159 HPC 245 sporadic 222 controls	no association	152
SRD5A2	L89V	Caucasian	288 sporadic 700 controls	VV OR 1.84 (1.15, 2.92)	19
SRD5A2	V89L	90% Caucasian 8% Afr Amer	440 sporadic 480 controls	OR 1.56 (p 0.02 Earlier diagnosis OR 2.35 ($p < 0.001$)	20
SRD5A2	A49T, L89V, (TA)n	Italian			153
SRD5A2	V89L	Italian	103 sporadic 109 controls	LL poor prognosis	21
UGT2B15	D85Y	Caucasian	155 sporadic 155 controls	OR 2.7 (1.1, 6.6)	28
UGT2B15	D85Y	Caucasian	200 sporadic 178 controls	DD OR 2.04 with high Gleason score	30
UGT2B15	D85Y	Caucasian	190 sporadic 190 controls	no association	29
Vitamin D					
VDR + UV	CDX-2 GA/AA Fok1 FF		368 sporadic 243 BPH	OR 2.11 OR 2.91	34
VDR	Activity alleles FokI FF or Ff TaqI	Caucasian nonHispanic	426 sporadic 440 controls	Significant with sun exposure tt	35

	BglI BB				
VDR	BsmI	Chinese	103 sporadic 106 control	no association	154
VDR	5132T/C	Afr Amer Caucasian	165sporadic 324 controls 93 sporadic 110 controls	VDR 5132C in Afr Amer OR=1.83 (1.02, 3.31)	155
VDR	FokI	Indian	128 sporadic 147 controls	FF p= 0.003	36
VDR	608906.A, 27823CT/g	Caucasian	812 sporadic 713 controls	no association	156
VDR	BamIbb	Caucasian	559 sporadic 523 controls	OR 1.49 (1.02, 2.17)	157
VDR	TaqI	Caucasian	288 sporadic 700 controls	no association	19
VDR	3' UTR	Brazilian	165 sporadic 200 controls	no association	158
VDR	Bam1, ApaI, TaqI	Japanese	81 HPC 105 controls	no association	159
VDR	FokI	Caucasian	191 sporadic	ff OR 0.76 (0.44, 1.32) with high grade	37
VDR + IGFBP3 levels	Fok1	Chinese	191 sporadic 304 controls	ff 0.14 (0.04, 0.56) IGFBP3 highest levels	38
VDR	TaqI	Austrian Caucasian	190 sporadic 190 controls	TT has OR of 1.76 (0.90, 3.45) not significant	160
VDR	TaqI	European	163 sporadic 211 controls	T allele OR 2.1 (1.15, 3.88)	161
VDR + UV	Haplotypes 4 SNPs	Caucasian	430 cancer 320 BPH	In men with low exposure to UV Two haplotype blocks associated with increased risk OR 1.95 (1.19, 3.20) OR 2.37 (1.38, 4.08)	39
Oxidative Stress					
GSTM1 GSTT1 GSTP1	meta analysis meta analysis meta analysis	multiethnic multiethnic multiethnic	2063 sporadic 2625 controls 1965 sporadic 2554 controls 2528 sporadic 3076 controls	no association no association no association	49
GSTM1 GSTT1 GSTP1 combined	null alleles null -313G	India	127 sporadic 144 controls	2.239 (1.37, 3.65) 1,891 (1.08 3;28) 2.48 (1.51, 4.08) 7.23 (2.42, 22.6)	45
GSTM1 + CYPA1	null	Japanese	115 sporadic 200 controls	2.2 (1.10, 4.57)	162
GSTA1 GSTT1 GSTA1 + GSTT1	AB/BB + smoking	Japanese	190 sporadic 294 controls	1.72 (1.01, 2.94) 1.68 (1.06, 2.68) 2.08 (1.06. 268)	51
GSTP1	I105V	Caucasian	122 sporadic 135 controls	Ile/Ile and smoking, OR 4.52 (1.07, 19.17)	46
GSTP1	I105V		483 HPC 499 sporadic 510 controls	no association	163
GSTP1	I/I		117 sporadic 183 controls	no association	164
GSTP1	I105V		105 sporadic 34 PIN 43 BPH	no association	165
GSTP1	(ATAAA)n	Caucasian	186 sporadic 398 controls	19 repeats, no significance	166
GSTM1	Null	Turkish	100 sporadic 107 controls	1.55 (0.72, 3.31)	133
GSTM1 GSTT1 GSTP1		Japanese	81 sporadic 105 controls	no association no association val/val OR 9.31 (0.47, 184) Null GSTM1 + GSTP1 val OR 2.67 (1.08, 6.59)	47
GSTM1 GSTT1 GSTP1		Finnish	206 sporadic 194 controls	null OR 0.64 (0.43, 0.95) no association no association	167
GSTM1 GSTT1 GSTP1		Caucasian	166 sporadic 166 BPH	no association no association *B (0.24 (0.09, 0.61)	48
GSTP1	I105V			I/I poor response	268
GSTM1 GSTP1 GSTT1	I105V		275 sporadic 280 controls	VV OR 1.8 (1.11, 2.91)	169
ADPRT	V762A	81% Cauc	522 sporadic	AA OR 2.65 (1.08, 6.49)	170

		19% Afr Amer	488 controls	VA OR 1.18 (0.85, 1.64)	
PPAR gamma	P12A	Finnish	193 sporadic 188 controls	no association	171
GPX1	GCG	Caucasian	267 sporadic 260 controls	A/A OR 1.67 (0.97, 287)	52
MnSOD	val/ala	Caucasian	567 sporadic 764 controls	AA genotype 0.3 (0.2-0.7)	53
MnSOD	Ala	Finnish (Caucasian)	197 sporadic 190 controls	ala OR 1.72 (0.96, 3.08)	172
Cell Cycle					
p53	pro/pro	Japanese	114 sporadic 105 controls	OR 2.8 (0.41 in higher grade)	173
p53	pro/pro	Caucasian	115 sporadic 181 controls	OR 0.23 (0.07, 0,79)	58
p53	pro/pro	Taiwanese	96 sporadic 126 controls	OR 2.6 (1.05, 6.4)	56
p53		Taiwanese	200 sporadic 181 BPH 247 controls	no association	59
p21	R31	Taiwanese	200 sporadic 181 BPH 247 controls	Arg/Arg OR 1.78 (1.06, 3.01)	59
HER-2	Val655Ile	Japanese	285 sporadic 233 controls	OR 0.476 (0.306, 0740)	174
TGFB1	L10P	Japanese	351 sporadic 221 BPH 303 controls	OR 1.62 (1.14, 2.30)	60
TGFB1	-C509T;T+29C	Caucasian	492 sporadic 492 controls	Late stages OR 2.4 at -509 TT	61
TGFBR1*6A		Caucasian	537 sporadic 488 controls	no association	62
TGFBR1*6A		multiethnic, 85% Cauc	442 sporadic 465 controls	no association	63
CDKN1B (p27)	79C/T		96 HPC	p 0.0005	175
CDK1A CDK1B	VV	Caucasian	96 sporadic 106 controls	CT/TT OR 2.24 (1.02, 4.95) OR 1.95 (1.09, 3.47)	176
TNF alpha	-308 promoter	Taiwanese	96 sporadic 126 controls	no association	56
CCND1 (cyclin D1)	A870G	Japanese	99 sporadic 115 controls	Familial AA vs AG GG OR 3.03 (1.11, 8.23)	64
CCND1	A870G	Japanese	214 sporadic 234 BPH 254 controls	AA OR 2.89 (1.38, 6.01)	65
PI3K	M326I	94% Caucasian	590 sporadic 495 controls	no association	177
PSA	PSA Promoter -158 A/G	Chinese	122 sporadic 84 BPH	OR GG to AG + AA 2.27 (p0.008)	40
PSA	-158, -252	Japanese	300 sporadic 216 BPH 266 controls	no association	43
PSA	-158 ARE	Japanese	101 sporadic 52 controls	No association with cancer GG associated with sensitivity to androgen ablation therapy	178
PSA	ARE polymorphism	Portuguese	151 sporadic 127 controls	A poor prognosis - AA OR 2.92 (1.10, 7.86)	42
PSA	ARE G allele	Caucasian	190 sporadic 190 controls	AG + GG OR 0.63 (0.39, 0.99)	41
PSA + AR	PSA haplotype AR CAG repeat PSA haplotype + AR CAG repeat	Caucasian and Afr. Am.	193 cases 160 Cauc. 33 Afr Am 391 controls 320 Cauc 71 Afr Am	PSA *2*2 haplotype OR 1.52 (076, 2.06) AR CAG repeat <20 repeats OR 1.46 (0.97, 2.19) PSA *2*2 + < 20 repeats Risk associated OR 4.27 (1.05, 20.75)	44
KLK2 (kallikrain-2)		84% Caucasian	190 sporadic 190 controls	TT OR 2.13 (1.3, 3.5)	179
KLK2	rs2664155 rs198977 haplotype of 5 SNPs	83.6% Caucasian	645 sporadic 606 controls	AG and AA OR 1.4 (1.2, 1.8) TT or CT OR 1.3 (1.1, 1.6) Haplotype OR 5.1 (1.6, 6.5)	180
KLK10	Codon 50 T/C		52 sporadic 49 control	GCC (p 0.027)	181
Adhesion					
E-cadherin	-160A/C	Japanese	219 sporadic 219 controls	no association	70
E cadherin	a/c -160	Japanese	236 sporadic 209 BPH	C+D classes OR 1.93	69

			139 controls		
E-cadherin (CDH1)	-160 C/A	Caucasian	82 sporadic 188 controls	AA associated with OR 3.6 (2.0, 6.4) (p 0.0004)	67
E-cadherin	A/C -160	Caucasian	1036 cases 669 controls	AA OR of 2.6 (1.4, 4.9) in HPC	66
E-cadherin	S270A	Caucasian	472 sporadic 159 HPC 923 controls	familial (p 0.01) sporadic (p 0.12)	71
E-cadherin	rs16260 (functional promoter polymorphism)	Swedish	157 HPC 1636 sporadic 801 controls	p 0.003 associated with positive family history	68
E-cadherin	-160 A/C	Caucasian Afr. Am.	86 sporadic 120 controls 49 sporadic 117 controls	AA associated with OR 3.04 (1.21, 7.32) AA OR 0.40 I 0.06, 2.00)	182
ICAM1	4 SNPs -9A/C K469E	Afr. Am.	108 familial 178 sporadic 391 controls	-9 A/C CC OR 2.5 (1.0, 6.3) K469E G OR 1.8 (1.1, 3.1) Haplotype (4 SNPs) OR 2.1 (1.4, 3.0) in familial cases	72
LPL	Ser447X	Japanese	273 sporadic 205 BPH 230 controls	OR 1.62 (1.07, 2.47) risk with CG + GG OR 2.30 (1.04, 5.08) with metastasis or high grade	183
DNA repair					
OGG1	11657A/G Ser326Cys	84% Caucasian 9% Afr Amer	159 HPC 245 sporadic 230 controls	Sporadic GG as risk p = 0.028 Hereditary GG as risk p = 0.03 Sporadic GG as risk p = 0.055	73
XRCC1	R399Q	Chinese	162 sporadic 251 controls	AA OR 2.18 (0.99 – 4.81)	74
MGMT	L84F	Chinese	162 sporadic 251 controls	CT + TT OR 1.99 (1.19-3.34)	74
NBS1	657del5	Polish	56 HPC 305 sporadic 1500 controls	OR 3.9 (p 0.0001)	75
DBNT3b DNA methyltrans-ferase	C/T	overall Afr Amer Caucasian	81 sporadic 42 BPH	OR 2.6 (0.8, 8.0) OR 4.3 OR 2.0	184
MTHFR	C677T A1298C	Afr Amer Caucasian	81 sporadic 42 BPH	OR 0.6 (0.3, 1.4) Het with C677T OR 0.3 (0.1, 1.1)	185
NAT2	M1, M2, M3	Japanese	111 sporadic 152 controls	Slow form at risk 2.21 (1.04, 4.69) Smoker, slow 2.78 (1.48, 9.66) Advanced slow 3.14 (1.40, 7.06) High grade slow 4.90 (1.97, 12.2)	186
Angiogenesis					
VEGF	-460 C/T	Chinese	96 sporadic 199 controls	T OR 2.3 (1.4, 3.0) TT OR 2.2 (1.3, 3.8)	76
FGF4	R388A	Caucasian Afr Amer	284 sporadic 97 controls 45 sporadic 94 controls	R p 0.005	78
HIF1A1	C1772T G1790A	Caucasian + Afr Amer	196 AIPC 196 controls	androgen independent prostate cancer p 0.024 C1772 no association G1790	77
Endostatin	4349G/A (D104N)	Caucasian	98 sporadic	no association	80
Endostatin	D104N	Caucasian/ Afr Amer	389 AIPC 352 controls	no association	81
ecNOS	E298D	Portuguese	161 sporadic	GG high grade tumor OR 6.15 (1.56, 24.17)	79
TMPRSS2	M160V	Caucasian	559 sporadic 523 controls	GG OR 2.05 (1.3, 3.2)	11
Leptin	-2548G/A	Caucasian	150 sporadic 118 controls	A with PrCa OR 1.6 Risk AA 2.93, AG 2.11 Advanced AA OR 2.58 AA+AG OR 4.67	187
OBR (leptin receptor)	L109R Q23R	Caucasian	271 sporadic 277 controls	not significant	91
IGF1	CA19	91% Caucasian 8% Afr Amer	440 sporadic 480 controls	no association	82
IGF1	CA19 repeat	Multiethnic	591 sporadic 538 controls	no association	83
IGF1	CA19	Caucasian Afr Amer	100 sporadic 93 controls	19R/19R OR 0.3 (0.1, 0.7)	84
IGF1	CA19	Japanese	303 sporadic 219 BPH	19R/19R OR 3.36 (1.30, 8.67)	188

			262 controls		
IGF1	Haplotype of 9 SNPs	Swedish	2836 sporadic 1737 controls	Haplotype OR 1.45 (1.15, 1.84)	86
IGF1	64 SNPs	Multiethnic	2320 sporadic 2290 controls	Haplotype 1B OR 1.21 (1.04,1.40) Haplotype 2C OR 1.24 (1.06, 1.44) Haplotype 3C OR 1.25 (1.03, 1.50) Haplotype 4D OR 1.19 (1.02,1.39)	85
IGFBP3	-202 A/C	91% Caucasian 8% Afr Amer	440 sporadic 480 controls	no association	82
IGFBP3	-202A/C	Japanese	307 sporadic 221 BPH 227 controls	C allele – aggressive disease	87
IGFBP3	-202A/C	Caucasian Afr Amer	100 sporadic 93 controls	no significant association	84
INS	+1127Pst	Afr Amer Caucasian	126 sporadic 126 controls	CC 2.15 (p0.008)	88
INS	+1127Pst	97% Caucasian	199 sporadic 267 controls	no association	89
IRS1	G972R	97% Caucasian	199 sporadic 267 controls	GR/RR OR 2.8 (1.5, 5.1)	89
IL-6	-174G\C		95 sporadic	more aggressive type	189
C2GnT	152A/G	Japanese	327 sporadic 235 BPH 301 controls	GG OR 3.60 AG OR 1.5	190
Genes associated with response to treatment					
HSD17B		Japanese	44 sporadic	Variants associated with side effect of EMP	191
COX2	-1285A/G, -1265G/A, -899G/C, 297C/G	Afr Amer Bini Nigerian Eur Amer	124 sporadic 164 control 154 sporadic 110 control 92 sporadic 92 control	Cancer risk -297G Afr Amer and Eur Amer OR 0.49 (0.2, 0.9) -1265A Afr Amer OR 2.72 (1.3, 5.8) -899C Afr Amer OR 3.67 (1.4, 9.9)	192
COX2	16 SNPs	Swedish	1378 sporadic 782 controls	rs20432 TG OR 0.78 (0.64, 0.98) rs689470 CT OR 0.66 (0.46, 0.96) one haplotype p 0.036 associated with decreased risk	193
Osteocalcin	C/T HindIII	Chinese	96 sporadic 132 control	Association with treatment response	194
Loci identified by prostate family studies					
ELAC2					
	S217L A541T E622V	Caucasian	150 sporadic 170 controls	LL =+ SL vs SS OR 1.54 (0.99, 2.41) no association no association	92
	S217L A541T E622V	Eur Amer Afr Amer	888 sporadic 473 controls 131 sporadic 163 controls	no association no association no association	96
	S217L A541T	Japanese	81 sporadic 106 control	no association no association	97
	S217L A541T	Japanese	350 sporadic 242 control	prostate cancer risk	95
	A541T	Japanese	285 sporadic 233 control	OR 4.02 (1.50, 10.8)	100
	S217L A541t	Caucasian (Australian)	825 sporadic 732 control 825 sporadic 732 control	no association no association	98
	S217L A541T	Caucasian	591 sporadic 538 control	one L 1.34 (1.02, 1.76) Two Ls1.73 (1.08, 2.77) no association	93
	A451T	Caucasian (British)	262 sporadic 469 control	no significance	101
	S217L	Japanese	98 sporadic 143 BPH	L OR 3.11 (1.22, 7.90)	94
	E622V	Finnish	467 sporadic 107 HPC 568 control	OR 2.94 (1.00, 8.23)	99
RNASEL					
	R462Q	Finnish	116 HPC 492 sporadic 223 BPH 566 control	1.96 p = 0.07 in HPC	103
	R462Q	Afr Amer Caucasian	131 sporadic 163 control 888 sporadic	OR 14.8 (1.6, 135) in Afr Amer OR 1.5 (1.04, 2.2) in low grade	96

			473 control		
	D541E E265X R462Q	Caucasian Afr Amer	885 sporadic 473 control 131 Afr Amer 163 control	EE vs DE + DD 1.68 (1.04, 2.70) no association no association	92
	4171 del AAAG	Ashkenazi	122 sporadic 437 control	no association	108
	G282A R462Q D541E	Japanese	100 sporadic 105 control	Q not in cases DD OR 7.37 (P= 0.004) D high grade OR 3.07 (p=0.14)	104
	I97L R462Q		438 HPC 510 control	not associated with sporadic Gln 0.54 (0.32, 0.91) low grade cancer	195
	E265X D541E	Caucasian (Swedish)	1624sporadic 801 controls	no association OR 0.77 (0.59, 1.00)	106
	4171 del AAAG	Ashkenazi non-Ashkenazi	85 sporadic 233 controls 34 sporadic 100 controls	OR 3.0 (0.6, 15.3) in Ashkenazi	107
	R462Q	Multiethnic	Sib pairs and 423 sporadic 454 controls	p (0.007) at least one copy OR 2.12 (1.19, 3.78)	196
	I97L, R462Q, D541E	Caucasian	136 HPC 227 sporadic 207 controls	no association	102
MSR1					
	P275A R293X aIVS5-59c	Caucasian	150 sporadic 170 controls	no association no association no association	92
	R293X IVS7delTTA	Afr. Amer Caucasian	131 sporadic 163 control 888 sporadic 473 control	OR 4.0 in high grade with negative family hist. OR 2.9 – 5.2 (depending on stage	96
	Mutations	Caucasian/ Afr Amer	159 HPC 249 sporadic 222 control	mutants are associated with PrCa	197
	999C>T (R293X)	Metanalysis	401 HPC 1982sporadic 2870 controls	OR 1.3 (0.93, 1.84)	110
LZTS1	8 SNPS		159 HPC 245 sporadic 222 controls	4 SNPs p> .004	198
KLF6	IVS1 splice	93% Caucasian	882 HPC 1253sporadic 1276 controls	increased risk (p<0.04) OR 1.42 (1.10, 1.80)	199
ATM	5557G>A 5558 A>T Ivs 38-30 t>c Ivs 38-15 g>c 3161G	Caucasian	637 sporadic 445 controls	no association no association no association no association OR 2.13 (1.17, 3.87)	111
CHEK2	mutation screen	Caucasian	578 sporadic 149 HPC 372 control	28 mutants in 578 cancers	9
CHEK2	1100delC I157T	Caucasian (Finnish)	230 HPC 537 sporadic 480 controls	1100delC OR 3.14 (0.65, 15) sporadic 1100delC OR 8.24 (1.49,45) HPC I157T OR 1.48)0.89,2.46) sporadic I157T OR 2.12 (1.06, 4.27) HPC	8
CHEK2	IVS2+1G-A 1100delC Truncating mutation I157T	Caucasian	690 sporadic 4000 controls	OR 2.5 (p 0.05) OR 1.7 (p 0.2) OR 2.2 (p0.4 OR 1.7 (p 0.002)	7
BRCA2	many SNPs	Caucasian	263 early onset	2% of early onset PrCa	6
FH	germline mutations		160 sporadic	no association	200
PTEN	IVS4		600 sporadic 803 controls	no association	113
PTEN	IVS4		248 sporadic 293 controls	no association	112
PTEN	17 SNPs	Multiethnic	2320 sporadic 2290 controls	Haplotype 4 homozygotes OR 2.70 (1.13, 6.47)	201

PrCa – prostate cancer, Cauc – Caucasian, Afr. Amer.- African American, OR - odds ration, CI – confidence interval, HPC – hereditary prostate cancer, Eur Amer. – European American

3.5. UDP-glucuronosyltransferase (UGT) 2B15 (UGT2B15)

The UGT2B15 gene codes for a protein that inactivates dihydrotestosterone rendering it water soluble. A functional variant of this protein (D85) has a lower Vmax of glucuronidation than the Y85 variant for the substrates alpha-androstanediol (alpha-diol) and dihydrotestosterone (DHT) (27). Three studies in Caucasians have investigated genetic polymorphisms of this gene. In one study the odds ratio was 2.7 for prostate cancer risk (28) while another found no association with increased prostate cancer risk (29). A third study found an association of the DD genotype with a high Gleason score (30).

3.6. Estrogen Receptor (ER)

The estrogen receptor has also been examined as a potential risk factor for prostate cancer. Estrogen receptor β has two SNPs of four examined that have a significant association with prostate cancer risk (31). ERα has a (GGGA)n repeat that Cancel-Tassin *et al* associated people who were homozygous for 5 repeats were at risk for prostate cancer (32). A polymorphism at T10C is associated with prostate cancer risk with CC having an odds ratio of 3.26 (1.58, 6.73, 95% CI) (33). Hernandez *et al* (2006) reported the association of ESR1 with prostate cancer risk in African Americans.

3.7. Vitamin D receptor (VDR)

Vitamin D is another steroid with an antiproliferative function that is relevant to prostate cancer carcinogenesis. The proliferative properties of vitamin D are regulated by its interaction with the receptor which then exerts an antiproliferative effect. Several polymorphisms have been identified in the receptor. The Fok1 polymorphism has been studied by a number of groups (34, 35, 36, 37, 38). In general the expression of the ff allele is associated with less cancer risk and an improved prognosis. However, UV exposure or other factors including genetic background can increase the odds ratio (35, 37, 38, 39). Other polymorphisms are quite variable from population to population (see Table 1).

3.8. Prostate Specific Antigen (PSA)

A SNP in the androgen response element of the promoter of the PSA gene (-158 A/G) has been examined by a number of individuals. In those studies that have found an association, the GG allele is connected with prostate cancer risk and a poor prognosis (40, 41, 42). However, one study in the Japanese population (43) did not find a correlation. Sieh *et al* concluded that there was a synergistic effect between PSA and the androgen receptor genotypes (44).

4. OXIDATIVE STRESS

4.1. Glutathione S transferase (GSTP1, GSTM1, and GSTT1)

Oxidative stress may be caused by endogenous and exogenous risk factors and is further regulated by pro-oxidant and antioxidant enzymes. The glutathione S transferases are a class of detoxification enzymes and reduce oxidative stress by interacting with oxygen free radicals. Consequently, mutations that decrease the function of these genes have been considered cancer susceptibility loci. GSTP1 most consistently correlates with prostate cancer risk (45, 46, 47, 48). However, risk assessment studies of this antioxidant marker show no association (see Table 1). Meta-analysis of GSTM1, GSTP1, and GSTT1 by Ntais did not correlate with prostate cancer risk (49). However, it is interesting that methylation of the GSTP1 locus is frequently observed early in prostate cancer (50), The most powerful data from the GST family are those that consider more than one gene at a time. Srivastiava *et al* demonstrated an odds ratio of 7.23 (CI 2.42, 22.6) in the Indian population when considering the combination of alleles for GSTM1, GSTP1, and GSTT1 (45). There have also been studies associating specific alleles in smokers with prostate cancer risk (46, 51). Another gene involved in oxidation is glutathione peroxidase (GPX). A study by Kote-Jarai *et al* in Caucasians indicated that the Ala/Ala at amino acid 6 form is associated with early onset prostate cancer risk (52).

4.2. Manganese superoxide dismutase (MnSOD)

MnSOD is an enzyme which reduces oxygen free radicals. MnSOD has been studied in two groups of Caucasians. However, in one study, the homozygous alanine genotype was associated with prostate cancer risk (Woodson *et al.*, 2003) while in the second study there was a protective effect. (53).

5. CELL CYCLE AND TUMOR SUPPRESSOR GENES

5.1. p53

P53 is perhaps the most mutated gene in cancer (54). A fairly common polymorphism at codon 72 has been associated with a functional difference (55). Two studies in Asian populations indicated that proline at codon 72 was associated with a high prostate cancer risk (56, 57). However, Henner *et al* found the opposite allele associated with prostate cancer in Caucasians (58). Moreover, another study in Taiwanese did not confirm an association (59). In the same study, the investigators established a connection between a variant of p21 and prostate cancer (59).

5.2. Transforming Growth Factor β

Variants of TGFβ have been examined for association with prostate cancer risk. The nonsynonymous substitution L10P has an odds ratio of 1.62 in the Japanese population as determined by Li *et al* (60). A study by Ewart-Toland *et al* in Caucasians indicated that other polymorphisms were associated with late stages of pro state cancer (61). In contrast, two studies with polymorphisms of the type I TGFB receptor did not have any detectable association with prostate cancer (62, 63).

5.3. Cyclin D1

Cyclin D1 is an important regulator of the cell cycle and has been implicated in a number of cancers. Two studies have been done in the Japanese population on a SNP that results in an amino acid change (A870G). Both find the AA allele is associated with prostate cancer risk (64, 65).

6. CELL ADHESION

Disruption of cellular adhesion is a key step in carcinogenesis. The E-cadherin (CDH1) has an important role in cell-cell adhesion. Some interesting polymorphisms have been detected that alter the function characteristics of E-cadherin. The A/C polymorphism at -160 has been shown to be associated with decreased transcription levels. This polymorphism has been associated with prostate cancer (66, 67, 68) a poor prognosis (69). However, one study in a Japanese population did not confirm the association (70). A second polymorphism (S270A) that results in a nonsynonymous amino acid change (71) is also related to familial prostate cancer.

ICAMs are intercellular adhesion molecules some genes of which are clustered on chromosome 19. Chen *et al* examined several SNPs in this region in African American prostate cancer cases and controls(72). Interestingly, ICAM1 SMPS -9A/C and K469E were associated with prostate cancer risk in men with a family history of prostate cancer.

7. DNA REPAIR

DNA repair is highly relevant to the initiation and promotion of cancer. Inherited susceptibility polymorphisms have been identified in several DNA repair genes.

7.1. 8- oxoguanine DNA glycosylase (OGG1)

OGG1 is a protein active in base excision DNA repair. Two polymorphisms have been examined: 11657 A/G and Ser326Cys (73). The 11657 SNP is significantly associated with prostate cancer risk in both hereditary and in sporadic cases. In contrast, the Ser326Cys polymorphism only shows significant risk in sporadic cases.

7.2. X-ray repair complementary group 1 (XRCC1) and O^6 methylguanine-DNA methyltransferase (MGMT)

XRCC1 and MGMT were analyzed in a Chinese population by Ritchey *et al* (74). The nonsynonymous variants R399Q of XRCC1 and L84F of MGMT both were associated with an increased risk of prostate cancer.

7.3. Nijmegen breakage syndrome (NBS1) or nibrin (NBN)

This DNA repair gene is mutated in Nijmegen breakage syndrome. The mutation 657del5 was found in both familial and nonfamilial cases of prostate cancer by Cybulski *et al* (75).

8. ANGIOGENESIS

8.1. Vascular endothelial growth factor (VEGF)

VEGF has been associated with a variety of cancers since it is a key molecule in angiogenesis. The -460 C/T polymorphism has been studied in the Chinese population. The presence of a single T or two T alleles had significant odds ratios for prostate cancer risk [2.3 (CI 1.4, 3.0) and 2.2 (CI 1.3, 3.8), respectively] (76).

8.2. Hypoxia-inducible factor 1, alpha subunit (HIF1A)

HIF1A is a regulator of the synthesis of VEGF. A study of androgen independent prostate cancers by Chau *et al* indicated an association with hormone refractory prostate cancer with the C1772 variant but not the G1790 variant (77) of the alpha subunit of HIF1A.

8.3. Fibroblast growth factor 4 (FGF4)

A coding variant in FGF4 (R388A) was assayed in Caucasian and African American men. In Caucasian men the arginine allele was associated with both prostate cancer risk and the occurrence of lymph node involvement (78).

8.4. Endothelial nitric oxide synthase (ecNOS)

A study of 161 sporadic cases implicated a SNP in ecNOS as an important factor in prostate cancer (79). The men with the glu/glu genotype at the E298D variant had an odds ratio of 6.15 (95% CI 1.56, 24.17) for having a high grade tumor.

8.5. Endostatin

A variant of endostatin was examined in men with sporadic cancer (80) and men with androgen independent prostate cancer (81). In contrast to the other genes involved in angiogenesis, neither study found an association of this molecule with prostate cancer.

9. METABOLIC MARKERS

9.1. Insulin-like growth factor 1 (IGF1)

Upregulation of IFG1 has been observed in prostate cancer tissue and in the serum of patients with prostate cancer. A CA repeat in the promoter region of IGF1 has been genotyped in men from various populations with prostate cancer. Two studies do not show a significant association (82, 83). However, one study in Japanese found an association of homozygosity of 19 repeats with prostate cancer (OR = 3.36 (CI 1.30,8.67), while another study of Caucasians and African American had the opposite result (CA19/CA19 – OR = 0.3 (0.1, 0.7) (84). Two studies with multiple SNPs have found small but significant associations of prostate cancer risk with specific haplotypes in the IGF1 locus (85) (86).

9.2. Insulin-like growth factor binding protein 3 (IGFBP3)

A promoter polymorphism in IGFBP3 (-202A/C) was examined by three groups (84, 82, 87). None of the studies showed a correlation of this polymorphism with prostate cancer risk, but Wang *et al* did find a connection with the C allele and aggressive disease.

9.3. Insulin (INS)

A PstI polymorphism at the insulin locus (+1127Pst) was reported by one group to have significant correlation of the CC genotype with prostate cancer (OR = 2.14, p 0.008) (88). A second group did not confirm this observation (89).

9.4. Insulin receptor substrate-1 (IRS1)

Neuhausen *et al* (2005) also studied a nonsynonymous polymorphism in IRS1 (G972R). They

found prostate cancer risk was associated with either GR or RR genotypes with an odds ratio of 2.8 (CI 1.5, 5.1) (89).

9.5. Leptin

Leptin has a polymorphism at -2548 that is associated with prostate cancer in Caucasians, especially in advanced disease (AA has an odds ratio of 2.58 while AA plus AG has an OR of 4.67) (90). However no significant association was found with variants of the leptin receptor (91).

10. COMMON VARIANTS IN FAMILIAL PROSTATE CANCER GENES

It is logical to hypothesize that variants of genes mutated in familial prostate cancer may be genetic factors in sporadic cancers. Several common polymorphisms have been reported for inherited genes in familial prostate cancer and their relevance to sporadic cancer has been investigated.

10.1. ELAC2

Three amino acid variants have been described for ELAC2: S217L, A451T, and E622V. Studies indicate that the L allele of S217L is associated with prostate cancer risk in Caucasians (92, 93) and in Japanese (94, 95). However, three other large studies did not confirm a significant relationship (96, 97, 98). The E622V polymorphism had a significant odds ratio of 2.94 in a Finnish population (99), but two other studies did not yield the same observation (92, 96). Only two studies confirmed an association of prostate cancer with the A541T variant (95, 100), while most others did not (92, 96, 97, 98, 93, 101).

10.2. RNASEL

Six polymorphisms in the RNASEL locus have been studied in prostate cancer. Four polymorphisms (R462Q, D541E, G282A, and I97V) code for amino acid changes. R462Q has been examined in a number of populations. The results vary from no association (92, 102) to a risk for the Q allele (103, 96) in contrast to a protective effect of the A allele (104, 105). Similar mixed findings have been made with D541E (92, 104, 106, 102). The work of Urisman *et al* suggests that specific RNASEL genotypes may allow the growth of certain viruses (4).

I97L has no association with sporadic prostate cancer (105, 102) nor does G282A (104). E265X results in a stop codon. However, the two studies that have examined this variant have concluded there is no association of E265X with prostate cancer (92, 106).

Conflicting reports exist for the 4171 del AAAG polymorphism in the Ashkenazi population. Rennert *et al* found an odds ratio of 3.0 (107) while Kotar *et al* found no association (108). 4171 del AAAG appears to be a founder mutation in this population.

10.3. MSR1

Macrophage scavenger receptor 1 has been implicated as a candidate for hereditary prostate cancer. Several studies show association of variants with prostate cancer (96, 109, 110). However, Noonan-Wheeler *et al* did not observe any association (92).

11. OTHER CANCER SYNDROME GENES

There are genes that have been associated with other cancers that have been examined for an association with prostate cancer. Four that have been tested are BRCA2, ATM, CHEK2, and PTEN.

11.1. Breast cancer gene (BRCA2)

A study of 263 early onset prostate cancer cases analyzed the coding region of BRCA2 for mutations (6). The investigators conclusion was that 2% of the early onset cases had germline changes.

11.2. Ataxia telangiectasia mutated (ATM)

Five polymorphisms in the ATM gene were genotyped in 637 sporadic cases and 445 controls (111). One of the SNPs 3161G, which codes for an amino acid change, was associated with prostate cancer risk having an odds ratio of 2.13).

11.3. Checkpoint kinase 2 (CHEK2)

CHEK2 was examined for mutations in 578 sporadic cancers (9) Of this group of men, 28 had germline mutations in CHEK2. In a study of 1100delC and I157T in the Finnish population, it was found that there was statistical significance only in hereditary prostate cancer, not sporadic (8). Another study in European Caucasians indicated that the IVS2+1 G-A and I157T polymorphisms are associated with risk for sporadic prostate cancer (7).

11.4. PTEN

PTEN loss is seen in prostate tumors. To determine whether germline variants had an association with prostate cancer, two studies investigated the variant in the intervening sequence – IVS4. Neither study found an association (112, 113).

12. PERSPECTIVE

1. The studies of SNPs in prostate cancer have resulted in consistent conclusions in some cases. Sample size coupled with allele frequency can greatly influence the validity of results. Many of the SNPs that have been studied have only minor effects on prostate cancer risk or outcome. Consequently, limited sample size or rare polymorphisms could greatly skew the results.

2. A second conclusion is that SNP associations can be population dependent. First, a given population may have a different interacting genetic background that influences particular polymorphism. Next, a SNP may not be the actual cause of prostate cancer risk or prognosis. The marker may be in linkage disequilibrium with the marker. The blocks and extent of linkage disequilibrium may vary from population to population.

3. The population differences seen in SNPs may in fact be due to effects other than genetic. For example, the prostate cancer effects may be due to exposure to an environmental

carcinogen or pathogen. The response of an individual may depend on their genetic makeup.

4. More information may be obtained from haplotyping multiple markers in the same region. Many of the experiments that have been done have been with individual SNPs. In fact, what may be important is the combination of markers in a region. As mentioned above, it may not be the markers themselves, but rather a neighboring genetic difference. Consequently, the haplotype will give a more accurate picture of the genetic locale of a genetic variant. The development of the HapMap (114) should aid in defining haplotypes.

5. There is no doubt that inherited genes are relevant to the development of prostate cancer. However, the analysis of these genes may be much more complicated than originally expected. There may be many genes that interact or certain combinations of genetic variants that are key in the development and progression of prostate cancer. A recent example is the study of Bettoun *et al* that indicate the interaction of androgen receptor and RNASEL is modified depending on the genotype of the individual (115). From the studies done to date there is mounting data suggesting the importance of genes: however, to fully understand the interactions between genes or sets of genes, better analysis tools may need to be developed.

6. The markers analyzed to date are logical candidates based on what is known about operative signaling pathways, but they may not be the best candidates. Just as genome wide linkage studies are useful for hereditary prostate cancer (116), whole genome association studies (117) may yield information on unexplored regions of the genome that have more impact on prostate cancer risk and development.

7. In addition the ultimate function of genetic mutations in many instances is influenced by epigenetic regulation and post translational modification adding a new dimension to the regulation of the functional phenotype. Ultimate understanding of the significant of SNPs will have to be interpreted in the context of not only the amount of protein or modified protein in the context of the molecules functionality that is in some cases will be regulated by the mutational event.

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Abbreviations: SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval, HPC: hereditary prostate cancer

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