TITLE:

Vitamin D Pathway Gene Variants and Prostate Cancer Risk

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Abstract

Vitamin D has antiproliferative, antiangiogenic, and apoptotic properties. There is some evidence supporting an association between vitamin D-related gene variants and prostate cancer risk. We report results from this population-based case-control study of genes encoding for the vitamin D receptor (*VDR*), the vitamin D activating enzyme 1-α-hydroxylase (*CYP27B1*) and deactivating enzyme 24-hydroxylase (*CYP24A1*). Forty-eight tagging single nucleotide polymorphisms (tagSNPs) were analyzed in 827 incident prostate cancer cases diagnosed in 2002 through 2005 and 787 age-matched controls. Contrary to some earlier studies, we found no strong evidence of altered risk of developing prostate cancer overall or within clinical measures of tumor aggressiveness for any of the tagSNPs when they were assessed individually or in haplotypes.

Introduction

Vitamin D has been shown to reduce cellular proliferation, increase apoptosis, and inhibit angiogenesis [1;2]. The link to prostate cancer (PCa) is supported by ecological studies demonstrating an inverse relationship between PCa incidence and ultraviolet (UV) exposure, which is the primary source of vitamin D[3]. Serum studies, which have provided inconsistent results for a relationship between vitamin D status and PCa risk, may not capture the relevant exposure period since not only does prostate carcinogenesis most likely begin decades prior to measurement, but 1-α-hydroxylase, the enzyme that activates vitamin D, is down-regulated early in the neoplastic process of PCa cells [4-6].

This study performed a comprehensive analysis of three genes in the vitamin D metabolism pathway: C*YP27B1,* encoding for 1-α-hydroxylase, which converts into the active form of the hormone 1,25-dihydroxy-vitamin D [1,25$(OH)_2$D]; *VDR*, encoding for the nuclear vitamin D receptor, which mediates all functions of 1,25$(OH)_2$D; and, C*YP24A1*, encoding for 24-hydroxylase, which catabolizes 1,25$(OH)_2$D into its excretion product. This population-based case-control study was completed to follow-up on our prior study which reported for two VDR loci, rs2107301 and rs2238135, carriers of the less common allele had higher risks of PCa [OR 2.47 (95% CI 1.52-4.00) and OR 1.95 (95% CI 1.17-3.26), respectively] and reported no association with PCa risk for the most frequently studied *VDR* polymorphisms *FokI* (rs10735810), *BsmI* (rs1544410), *ApaI* (rs7975232), and *TaqI* (rs731236)[7].

Materials and Methods

Study Population

Study subjects were enrolled in a population-based prostate cancer case-control study that has been described previously[8]. Eligible individuals were Caucasian or African American men. Cases were diagnosed with histologically confirmed prostate cancer between ages 35-74 years from January 1, 2002 to December 31, 2005. Prostate cancer cases were identified from the metropolitan Seattle-Puget Sound population-based tumor registry that is operated as part of National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Of the 1,001 eligible interviewed cases, 827 (82.6%) had peripheral blood leukocyte samples collected. Eligible controls were recruited evenly throughout the ascertainment period for cases using random digit telephone dialing (RDD) and frequency matched to cases by 5-year age

groups. Of the 942 eligible interviewed controls, 787 (83.5%) had peripheral blood leukocyte samples collected. This study was approved by Fred Hutchinson Cancer Research Center's Institutional Review Board and genotyping was approved by the Internal Review Board of the National Human Genome Research Institute.

SNP Selection and Genotyping

SNPs capturing genetic variability in the *VDR*[9] and *CYP27B1*[10] genes were selected using resequencing data, while SNP selection for *CYP24A1*[11] used publicly available data from the HapMap consortium[1]. SNP selection and genotyping duplicated methods described in the previous case-control study[7]. Percent agreement of blind duplicates was ≥98% for all tagSNPs.

Statistical Analysis

Statistical methods were identical to our previous study[7]. All SNPs, except for rs912505 in *CYP24A1*, were consistent ($P > 0.05$) with HWE among Caucasian controls. Data were analyzed using unconditional logistic regression to calculate odds ratios as estimates of relative risk of prostate cancer associated with SNP genotypes. We included age and stratified by race in all regression models. We assessed possible confounding effects of variables listed in Table 1 and found none appreciably altered risk estimates, thus did not include them as covariates. Global tests of association, which were estimated by comparing an adjusted model that included all SNPs for a given gene to the null model that only included adjustment covariates, automatically adjusted for multiple testing based on degrees of freedom of the corresponding χ_2 test[12]. Multiple comparisons were also accounted for by using permutations to calculate exact p-values for each significant individual SNP ($\alpha = 0.05$). All analyses were done using STATA statistical package (version 9.2, STATA Corp., College Station, TX).

Results

Cases and controls were similar in age (mean in cases, 61.7 years; in controls, 61.1 years). Cases had a higher percentage of African Americans, subjects reporting a family history of prostate cancer, and subjects with a history of PSA testing (Table 1). The majority of prostate cancers were local stage tumors with low/moderate Gleason scores.

[1] www.hapmap.org

There was no strong evidence of altered risk of developing prostate cancer for any tagSNPs evaluated (Table 2) or haplotypes (data not shown). In Caucasians two loci (*VDR*: rs4760674 and *CYP27B1*: rs4809960) showed slightly lower relative risks of prostate cancer for homozygous variant versus homozygous wildtype carriers [OR 0.68 (95% CI 0.48-0.95) and OR 0.77 (95% CI 0.62-0.96), respectively], but after adjusting for multiple comparisons these associations were no longer significant. Stratification by measures of tumor aggressiveness, such as Gleason score or stage, did not reveal significant associations of risk with genotypes. Lastly, there was no evidence of effect modification by total vitamin D or calcium intake.

Discussion

One goal of this study was to evaluate earlier findings by our group that showed *VDR* tagSNPs rs2107301 and rs2238135 to be significantly associated with prostate cancer[7]. We did not replicate our earlier findings or identify any additional genotypes associated with PCa risk in this comprehensive group of tagSNPs for *VDR, CYP27B1,* and *CYP24A1* genes. Our findings corroborate a lack of an association between PCa risk and frequently studied *VDR* polymorphisms *BsmI* (rs1544410), *TaqI* (rs731236), *Apa*I (rs7975232), and *FokI* (rs10735810)[7;13;14].

This study attempted to capture genetic variation within a pathway of genes. Assuming 80% power, the minimal detectable odds ratio was 0.46 or 1.76 for evaluating tagSNPs with a minor allele frequency of 5% or greater. We were underpowered to examine risk within African Americans, moreover, since polymorphic alleles in *VDR, CYP27A1* and *CYP24B1* differ by ethnicity and tagSNP selection was based on a Caucasian population, gene coverage for an African American population is not complete. We did not find any evidence that vitamin D intake was an effect modifier; however, we were unable to account for plasma vitamin D levels or UV light exposure.

Our findings suggest that common genotypic variation found in *VDR, CYP27A1* and *CYP24B1* has little or no effect on overall prostate cancer risk. Future studies may reveal that these genotypes effect disease progression rather than risk of developing disease.

Table 1. Distribution and risk estimates for selected characteristics of cases and controls, King County, Washington, 2002-2005

	Cases (%) (n=827)	Controls (%) (n=787)	Adjusted OR* (95% CI)
Age group			
35-49	78 (9.4)	76 (9.7)	
50-54	85 (10.3)	95 (12.1)	
55-59	147 (17.8)	149 (18.9)	
60-64	182 (22)	157 (19.9)	
65-69	177 (21.4)	164 (20.8)	
70-74	158 (19.1)	146 (18.6)	
Race			
Caucasian	711 (86)	718 (91.2)	1.00 (reference)
African American	116 (14)	69 (8.8)	1.79 (1.30-2.47)
First-degree relative with prostate cancer			
No	635 (76.8)	694 (88.2)	1.00 (reference)
Yes	192 (23.2)	93 (11.8)	2.27 (1.73-2.98)
Number of PSA tests†			
None	182 (22)	193 (24.5)	1.00 (reference)
1-2	138 (16.7)	144 (18.3)	1.04 (0.76-1.43)
3-4	143 (17.3)	112 (14.2)	1.43 (1.03-1.99)
≥5	312 (37.7)	207 (26.3)	1.70 (1.28-2.26)
Unknown	52 (6.3)	131 (16.6)	
Total vitamin D (ug/d) ‡			
≤ 6.9	188 (22.7)	190 (24.1)	1.00 (reference)
7.0-12.9	220 (26.6)	189 (24)	1.18 (0.89-1.57)
13.0-17.4	211 (25.5)	189 (24)	1.12 (0.85-1.49)
≥ 17.5	180 (21.8)	190 (24.1)	0.95 (0.72-1.27)
Unknown	28 (3.4)	29 (3.7)	
Stage of PCa at diagnosis			
Local	676 (81.7)		
Regional	134 (16.2)		
Distant	17 (2.1)		
Gleason score at diagnosis			
2-6, 7 (3+4)	674 (81.5)		
7(4+3), 8-10	148 (17.9)		
Unknown	5 (0.6)		

* Adjusted for age.
† PSA tests done in the previous 5 years before reference date.
‡ Total daily intake from diet and supplements.

Table 2. Genotype distribution and odds ratios (95% CI) for associations between *VDR* (vitamin D receptor), *CYP27B1* (1-alpha-hydroxlase) and *CYP24A1* (24-hydroxylase) genotypes and prostate cancer risk by race.

			Caucasians				African Americans			
			Cases (%)	Controls (%)	Adjusted OR†		Cases (%)	Controls (%)	Adjusted OR†	
Gene	**SNP**	**Genotype**	**(n=711)***	**(n=718)***	**(95% CI)**	**P_{trend}†**	**(n=116)***	**(n=69)***	**(95% CI)**	**P_{trend}†**
VDR	rs2544038	TT	218(31)	223(31)	1.00 (reference)		50(43)	24(36)	1.00 (reference)	
	Block A	CT	347(49)	363(51)	0.98 (0.77-1.24)		53(46)	33(49)	0.78 (0.39-1.59)	
	(23295bp 3′ of STP)	CC	140(20)	130(18)	1.10 (0.81-1.49)		12(10)	10(15)	0.57 (0.20-1.62)	
		CC+CT			1.01 (0.81-1.26)	*0.61*			0.73 (0.37-1.44)	*0.28*
	rs739837	TT	193(27)	202(28)	1.00 (reference)		43(37)	24(36)	1.00 (reference)	
	Block B	GT	367(52)	342(48)	1.12 (0.88-1.44)		55(48)	31(46)	1.26 (0.61-2.62)	
	(Ex11+568)	GG	143(20)	169(24)	0.88 (0.66-1.19)		17(15)	12(18)	1.09 (0.41-2.91)	
		GG+GT			1.04 (0.83-1.32)	*0.50*			1.22 (0.61-2.42)	*0.74*
	rs731236	TT	242(35)	261(37)	1.00 (reference)		58(51)	29(46)	1.00 (reference)	
	Block B	CT	349(50)	328(47)	1.15 (0.91-1.45)		45(39)	27(43)	0.71 (0.35-1.45)	
	(Ex11+32)	CC	106(15)	108(15)	1.06 (0.77-1.46)		11(10)	7(11)	0.64 (0.21-1.97)	
		CC+CT			1.13 (0.91-1.40)	*0.50*			0.70 (0.36-1.36)	*0.30*
	rs1544410	AA	239 (34.9)	255 (36.4)	1.00 (reference)		57 (51.4)	27 (40.9)	1.00 (reference)	
	Block B	AG	339 (49.6)	331 (47.2)	0.45 (0.87-1.38)		47 (42.3)	26 (39.4)	0.95 (0.50-2.10)	
	(IVS10+283)	GG	106(15.5)	115 (16.4)	0.92 (0.72-1.35)		7 (6.3)	13 (19.7)	**0.02 (0.09-0.80)**	
		GG+AG			0.58 (0.85-1.33)	*0.89*			0.41 (0.39-1.47)	*0.07*
	rs2239182	GG	188(27)	190(27)	1.00 (reference)		38(33)	25(37)	1.00 (reference)	
	Block B	AG	347(49)	340(48)	1.03 (0.80-1.32)		60(52)	34(51)	1.16 (0.57-2.36)	
	(IVS5+3419)	AA	167(24)	185(26)	0.91 (0.68-1.22)		17(15)	8(12)	1.04 (0.36-3.05)	
		AA+AG			0.99 (0.78-1.25)	*0.54*			1.14 (0.58-2.24)	*0.82*
	rs2107301§	CC	383(55)	369(53)	1.00 (reference)		76(67)	44(70)	1.00 (reference)	
	Block B	CT	265(38)	274(39)	0.93 (0.75-1.16)		34(30)	19(30)		
	(IVS5+3260)	TT	50(7)	54(8)	0.89 (0.59-1.34)		4(4)	0(0)		
		TT+CT			0.92 (0.75-1.14)	*0.45*			0.82 (0.40-1.71)	
	rs2239181	TT	542(79)	571(81)	1.00 (reference)		89(78)	52(78)	1.00 (reference)	
	Block B	GT	142(21)	126(18)	1.19 (0.91-1.55)		23(20)	15(22)		
	(IVS5+2881)	GG	5(1)	11(2)	0.48 (0.17-1.39)		2(2)	0(0)		
		GG+GT			1.13 (0.87-1.47)	*0.62*			0.57 (0.25-1.29)	

rs2238139	TT	404(57)	434(61)	1.00 (reference)		70(61)	38(57)	1.00 (reference)	
Block B	CT	270(38)	247(35)	1.17 (0.94-1.46)		41(36)	28(42)	1.04 (0.52-2.06)	
(IVS5+2550)	CC	30(4)	34(5)	0.94 (0.57-1.57)		4(3)	1(1)	4.72 (0.45-49.66)	
	CC+CT			1.15 (0.93-1.42)	*0.36*			1.13 (0.58-2.22)	*0.46*
rs3782905	CC	328(47)	344(49)	1.00 (reference)		68(61)	38(57)	1.00 (reference)	
Block B	CG	302(43)	301(42)	1.05 (0.84-1.31)		41(37)	27(40)	0.80 (0.41-1.59)	
(IVS4+6584)	GG	66(9)	64(9)	1.08 (0.74-1.58)		3(3)	2(3)	0.94 (0.13-6.66)	
	GG+CG			1.06 (0.86-1.30)	*0.59*			0.81 (0.42-1.58)	*0.59*
rs7974708	TT	303(43)	323(45)	1.00 (reference)		78(68)	43(64)	1.00 (reference)	
Block B	CT	322(46)	319(44)	1.08 (0.86-1.34)		33(29)	20(30)	1.23 (0.59-2.57)	
(IVS4+2586)	CC	79(11)	75(10)	1.12 (0.79-1.60)		4(3)	4(6)	0.62 (0.12-3.10)	
	CC+CT			1.08 (0.88-1.34)	*0.43*			1.13 (0.56-2.26)	*0.96*
rs11168275	AA	415(59)	406(57)	1.00 (reference)		46(40)	27(40)	1.00 (reference)	
Block B	AG	253(36)	268(37)	0.92 (0.74-1.15)		56(49)	34(51)	0.86 (0.43-1.72)	
(IVS4+476)	GG	37(5)	42(6)	0.86 (0.54-1.37)		13(11)	6(9)	1.51 (0.47-4.83)	
	GG+AG			0.91 (0.74-1.13)	*0.38*			0.95 (0.49-1.84)	*0.76*
rs10735810	GG	262(37)	263(37)	1.00 (reference)		65(57)	39(58)	1.00 (reference)	
No Block	AG	335(48)	352(49)	0.96 (0.76-1.20)		48(42)	24(36)	1.07 (0.54-2.12)	
(Ex4+4)	AA	108(15)	101(14)	1.07 (0.78-1.48)		2(2)	4(6)	0.19 (0.02-1.54)	
	AA+AG			0.98 (0.79-1.22)	*0.83*			0.95 (0.49-1.84)	*0.52*
rs2408876	TT	254(37)	232(33)	1.00 (reference)		32(28)	17(25)	1.00 (reference)	
Block C	CT	343(49)	356(51)	0.88 (0.70-1.11)		59(52)	34(51)	1.07 (0.49-2.35)	
(IVS3-667)	CC	96(14)	116(16)	0.75 (0.55-1.04)		22(19)	16(24)	0.85 (0.34-2.17)	
	CC+CT			0.85 (0.68-1.06)	*0.08*			1.00 (0.48-2.10)	*0.76*
rs2238135[§]	GG	404(58)	405(57)	1.00 (reference)		41(36)	25(38)	1.00 (reference)	
Block C	CG	255(37)	255(36)	1.00 (0.80-1.25)		55(48)	35(53)	0.79 (0.39-1.60)	
(IVS2-1633)	CC	34(5)	48(7)	0.71 (0.45-1.12)		18(16)	6(9)	1.64 (0.54-4.99)	
	CC+CG			0.96 (0.77-1.18)	*0.35*			0.91 (0.46-1.80)	*0.68*
rs10875694	AA	494(71)	475(68)	1.00 (reference)		82(73)	50(75)	1.00 (reference)	
Block C	AT	183(26)	206(29)	0.85 (0.67-1.08)		29(26)	16(24)	1.00 (0.46-2.14)	
(IVS2-5103)	TT	14(2)	21(3)	0.64 (0.32-1.28)		1(1)	1(1)	0.70 (0.04-11.62)	
	TT+AT			0.83 (0.66-1.05)	*0.09*			0.98 (0.46-2.07)	*0.91*

rs11168287	TT	159(23)	171(24)	1.00 (reference)		54(47)	36(54)	1.00 (reference)	
Block C	CT	359(51)	364(51)	1.06 (0.82-1.38)		53(46)	26(39)	1.64 (0.83-3.28)	
(IVS2-8206)	CC	180(26)	176(25)	1.10 (0.81-1.48)		8(7)	5(7)	1.26 (0.35-4.52)	
	CC+CT			1.07 (0.84-1.37)	*0.54*			1.58 (0.82-3.06)	*0.28*
rs7299460	CC	343(49)	350(49)	1.00 (reference)		9(8)	10(15)	1.00 (reference)	
Block C	CT	291(42)	309(43)	0.96 (0.77-1.20)		44(39)	26(39)	2.05 (0.68-6.23)	
(IVS1+2470)	TT	66(9)	54(8)	1.25 (0.85-1.84)		61(54)	31(46)	2.30 (0.78-6.81)	
	TT+CT			1.00 (0.81-1.24)	*0.57*			2.19 (0.77-6.19)	*0.20*
rs11168314	CC	418(60)	461(65)	1.00 (reference)		49(43)	34(51)	1.00 (reference)	
Block C	CT	253(36)	217(31)	**1.28 (1.03-1.61)**		51(45)	25(37)	1.45 (0.72-2.92)	
(-27390)	TT	23(3)	26(4)	0.98 (0.55-1.74)		13(12)	8(12)	1.62 (0.56-4.67)	
	TT+CT			**1.25 (1.01-1.56)**	*0.10*			1.49 (0.77-2.87)	*0.25*
rs4073729	CC	487(71)	512(73)	1.00 (reference)		68(61)	45(68)	1.00 (reference)	
Block C	CT	185(27)	175(25)	1.11 (0.87-1.41)		40(36)	21(32)		
(-20950)	TT	17(2)	19(3)	0.95 (0.49-1.85)		4(4)	0(0)		
	TT+CT			1.09 (0.87-1.38)	*0.55*			1.52 (0.76-3.05)	
rs4760674	CC	245(37)	248(36)	1.00 (reference)		57(53)	26(40)	1.00 (reference)	
Block C	AC	346(52)	326(47)	1.07 (0.85-1.36)		47(44)	33(51)	0.59 (0.29-1.19)	
(-1005)	AA	76(11)	114(17)	**0.68 (0.48-0.95)**		4(4)	6(9)	0.26 (0.06-1.16)	
	AA+AC			0.97 (0.78-1.21)	*0.11*			0.54 (0.27-1.07)	*0.04*
rs6823	CC	217(31)	213(30)	1.00 (reference)		53(46)	25(38)	1.00 (reference)	
Block C	CG	358(52)	347(49)	1.01 (0.80-1.29)		50(44)	31(47)	0.81 (0.40-1.64)	
(Ex7-250)	GG	118(17)	147(21)	0.79 (0.58-1.07)		11(10)	10(15)	0.63 (0.22-1.78)	
	GG+CG			0.95 (0.75-1.19)	*0.19*			0.76 (0.39-1.49)	*0.35*
rs2071358	CC	457(66)	470(67)	1.00 (reference)		54(48)	43(64)	1.00 (reference)	
Block C	AC	212(31)	212(30)	1.03 (0.82-1.29)		51(45)	20(30)	1.81 (0.90-3.64)	
(740bp 3' of STP)	AA	24(3)	22(3)	1.12 (0.62-2.02)		8(7)	4(6)	1.46 (0.38-5.58)	
	AA+AC			1.04 (0.83-1.29)	*0.70*			1.75 (0.90-3.40)	*0.16*
CYP27B1									
rs3782130	AA	637(92)	636(92)	1.00 (reference)		97(85)	54(86)	1.00 (reference)	
Block A	AC	50(7)	52(8)			15(13)	8(13)	0.89 (0.33-2.40)	
	CC	2(0)	0(0)			2(2)	1(2)	1.05 (0.09-12.46)	
	CC+AC			1.00 (0.67-1.49)				0.91 (0.35-2.32)	*0.82*

rs4646537	CC	319(45)	314(44)	1.00 (reference)		85(74)	50(75)	1.00 (reference)	
No Block	CG	324(46)	325(45)	0.98 (0.79-1.22)		28(24)	16(24)	1.16 (0.54-2.48)	
(IVS8+113)	GG	61(9)	77(11)	0.78 (0.54-1.13)		2(2)	1(1)	0.75 (0.06-9.98)	
	GG+CG			0.94 (0.76-1.16)	*0.30*			1.13 (0.54-2.37)	*0.82*
CYP24A1									
rs927650	CC	172(25)	181(25)	1.00 (reference)		62(54)	34(51)	1.00 (reference)	
Block A	CT	354(50)	373(52)	1.00 (0.78-1.29)		44(39)	29(43)	0.84 (0.43-1.67)	
(IVS11+967)	TT	175(25)	161(23)	1.15 (0.85-1.55)		8(7)	4(6)	1.30 (0.34-4.93)	
	TT+CT			1.04 (0.82-1.33)	*0.38*			0.90 (0.47-1.73)	*0.97*
rs912505	AA	468(67)	437(61)	1.00 (reference)		44(38)	26(39)	1.00 (reference)	
Block A	AG	212(30)	258(36)	**0.77 (0.61-0.96)**		51(44)	22(33)	1.74 (0.81-3.73)	
(IVS7-1179)	GG	23(3)	21(3)	1.02 (0.56-1.87)		20(17)	19(28)	0.85 (0.36-2.02)	
	GG+AG			**0.79 (0.63-0.98)**	*0.07*			1.33 (0.67-2.62)	*0.93*
rs6127118	GG	419(60)	425(60)	1.00 (reference)		61(53)	33(49)	1.00 (reference)	
Block B	AG	278(40)	287(40)			54(47)	34(51)		
(IVS7+204)	AA	0(0)	0(0)			0(0)	0(0)		
	AA+AG			0.98 (0.79-1.22)				1.02 (0.53-1.96)	
rs6068816	CC	558(80)	580(81)	1.00 (reference)		103(90)	62(93)	1.00 (reference)	
Block B	CT	135(19)	127(18)	1.11 (0.84-1.45)		11(10)	3(4)	1.84 (0.44-7.63)	
(Ex6+12)	TT	6(1)	5(1)	1.25 (0.38-4.11)		1(1)	2(3)	0.21 (0.02-2.69)	
	TT+CT			1.11 (0.85-1.45)	*0.42*			1.13 (0.35-3.71)	*0.75*
rs2762939	GG	380(54)	376(53)	1.00 (reference)		29(25)	13(19)	1.00 (reference)	
Block B	CG	272(39)	294(41)	0.92 (0.74-1.14)		48(42)	32(48)	0.66 (0.28-1.55)	
(IVS5-149)	CC	50(7)	45(6)	1.10 (0.72-1.68)		37(32)	22(33)	0.82 (0.33-2.03)	
	CC+CG			0.94 (0.76-1.16)	*0.83*			0.73 (0.33-1.60)	*0.75*
rs2244719	TT	209(30)	201(28)	1.00 (reference)		62(55)	38(58)	1.00 (reference)	
Block C	CT	328(48)	371(52)	0.85 (0.67-1.09)		41(36)	25(38)	0.97 (0.49-1.95)	
(IVS4-486)	CC	153(22)	136(19)	1.08 (0.80-1.46)		10(9)	3(5)	1.68 (0.41-6.87)	
	CC+CT			0.91 (0.73-1.15)	*0.78*			1.06 (0.55-2.05)	*0.66*
rs3787557	TT	528(75)	518(72)	1.00 (reference)		107(93)	61(91)	1.00 (reference)	
Block C	CT	168(24)	187(26)	0.88 (0.69-1.12)		8(7)	6(9)		
(IVS4-763)	CC	8(1)	12(2)	0.65 (0.26-1.61)		0(0)	0(0)		
	CC+CT			0.87 (0.69-1.10)	*0.19*			0.68 (0.20-2.33)	*0.54*

rs2181874	GG	406(58)	400(56)	1.00 (reference)		37(32)	22(33)	1.00 (reference)	
No Block	AG	249(35)	273(38)	0.90 (0.72-1.12)		56(49)	31(46)	1.22 (0.58-2.58)	
(IVS4+1653)	AA	48(7)	41(6)	1.15 (0.74-1.79)		22(19)	14(21)	0.83 (0.32-2.10)	
	AA+AG			0.93 (0.76-1.15)	*0.85*			1.09 (0.55-2.19)	*0.81*
rs4809960	TT	432(62)	387(56)	1.00 (reference)		93(83)	46(73)	1.00 (reference)	
Block D	CT	220(32)	260(38)	**0.76 (0.60-0.95)**		18(16)	17(27)		
(IVS4+58)	CC	45(6)	46(7)	0.87 (0.57-1.35)		1(1)	0(0)		
	CC+CT			**0.78 (0.63-0.96)**	*0.06*			0.48 (0.21-1.08)	
rs2296241	AA	170(25)	183(26)	1.00 (reference)		37(33)	15(23)	1.00 (reference)	
Block D	AG	356(51)	371(53)	1.03 (0.80-1.33)		50(45)	39(59)	0.49 (0.23-1.08)	
(Ex4+9)	GG	166(24)	151(21)	1.18 (0.87-1.61)		25(22)	12(18)	0.69 (0.26-1.85)	
	GG+AG			1.08 (0.85-1.37)	*0.28*			0.54 (0.26-1.15)	*0.35*
rs2245153	TT	485(69)	451(63)	1.00 (reference)		47(41)	31(46)	1.00 (reference)	
No Block	CT	192(27)	233(33)	**0.77 (0.61-0.96)**		57(50)	31(46)	1.29 (0.65-2.55)	
(IVS3-179)	CC	26(4)	31(4)	0.78 (0.46-1.33)		11(10)	5(7)	1.11 (0.32-3.82)	
	CC+CT			**0.77 (0.62-0.96)**	*0.03*			1.26 (0.65-2.43)	*0.60*
rs2585428	GG	218(31)	203(29)	1.00 (reference)		33(29)	19(30)	1.00 (reference)	
No Block	AG	348(50)	353(51)	0.92 (0.72-1.17)		48(42)	29(46)	1.03 (0.47-2.27)	
(IVS3-670)	AA	132(19)	141(20)	0.87 (0.64-1.18)		33(29)	15(24)	1.26 (0.52-3.08)	
	AA+AG			0.90 (0.72-1.14)	*0.36*			1.12 (0.54-2.31)	*0.61*
rs13038432	AA	593(86)	593(84)	1.00 (reference)		109(96)	66(99)	1.00 (reference)	
No Block	AG	87(13)	103(15)	0.85 (0.62-1.15)		5(4)	1(1)		
(IVS3+814)	GG	12(2)	8(1)	1.50 (0.61-3.70)		0(0)	0(0)		
	GG+AG			0.89 (0.67-1.20)	*0.70*			1.52 (0.17-13.95)	*0.71*
rs6022999	AA	413(58)	419(58)	1.00 (reference)		23(20)	7(10)	1.00 (reference)	
No Block	AG	253(36)	266(37)	0.97 (0.78-1.20)		47(41)	32(48)	0.77 (0.27-2.16)	
(IVS3+103)	GG	41(6)	32(4)	1.30 (0.80-2.10)		45(39)	28(42)	0.82 (0.29-2.32)	
	GG+AG			1.00 (0.81-1.24)	*0.67*			0.79 (0.30-2.10)	*0.82*

* Variable numbers of cases and controls reflect instances of failed genotyping.

† Adjusted for age. Odd ratios with a $p \leq 0.05$ are bolded. These did not remain significant after adjustment for multiple comparisons. If there are no case or control homozygote carriers of less common allele, then only dominant model risk estimate is shown.

‡ Analysis for linear trend according to the number of variant alleles. If there are no case or control homozygote carriers of less common allele this analysis is omitted.

§ These polymorphisms were found to be significantly associated with PCa risk in the prior study done by Holick et al[7].

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